ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Volume 65, Art. 5 Pages 357–652

Editor in Chief
Otto v. St. Whitelock

Associate Editor
Franklin N. Furness

MERCURY AND ITS COMPOUNDS

BY

Cecil V. King, Harry Gold, and Harold Wolff (*Conference Chairmen*), E. A. Brown, E. M. Butt, J. M. Evans, I. Feder, H. L. Friedman, E. Goldberger, L. J. Goldwater, C. L. Gordon, G. B. Gordon, I. J. Greenblatt, T. H. Greiner, G. C. Griffith, C. A. Handley, J. W. Hendrick, A. E. Hitchcock, W. L. Hughes, M. S. Klapper, W. E. Lawrence, W. A. Leff, W. N. Lipscomb, E. F. Lowry, J. H. Moyer, H. E. Nussbaum, G. W. Sears, R. A. Seibert, H. A. Shoemaker, R. E. Weston, E. Wichers, G. F Wright, P. W. Zimmerman.

Consulting Editor
Cecil V. King

NEW YORK
PUBLISHED BY THE ACADEMY
April 11, 1957

THE NEW YORK ACADEMY OF SCIENCES

(Founded in 1817)

COUNCIL, 1957

President
ROSS F. NIGRELLI

President-Elect
BORIS PREGEL

Vice-Presidents
EDWARD J. KEMPF
HILARY KOPROWSKI

Recording Secretary
EMERSON DAY

Corresponding Secretary
FREDERICK C. NACHOD

Treasurer
ROBERT F. LIGHT

Elected Councilors

1955–1957
M. J. KOPAC
C. P. RHOADS
LLOYD C. MILLER
ELMER L. SEVERINGHAUS

1956–1958
DONALD B. KEYES
WARREN O. NELSON
CHARLES D. MARPLE
FREDERICK Y. WISELOGLE

1957–1959
GEORGE H. MANGUN
MINA REES
HAYDEN C. NICHOLSON
WILLIAM W. WALCOTT

Finance Committee
HARDEN F. TAYLOR, *Chairman*
GORDON Y. BILLARD
JOHN TEE-VAN

Executive Director
EUNICE THOMAS MINER

SECTION OF GEOLOGY AND MINERALOGY
M. HALL TAYLOR, *Chairman* ANASTASIA VAN BURKALOW, *Secretary*

SECTION OF BIOLOGY
ALBERT S. GORDON, *Chairman* LOUIS G. NICKELL, *Secretary*

DIVISION OF MYCOLOGY
M. L. LITTMAN, *Chairman* KARL MARAMOROSCH, *Secretary*

SECTION OF PSYCHOLOGY
RALPH F. HEFFERLINE, *Chairman* ELAINE GRIMM, *Secretary*

SECTION OF ANTHROPOLOGY
MARGARET MEAD, *Chairman* DOROTHY CROSS JENSEN, *Secretary*

SECTION OF PHYSICS AND CHEMISTRY
ROBERT NEILSON BOYD, *Chairman* JOSEPH GREENSPAN, *Secretary*

SECTION OF OCEANOGRAPHY AND METEOROLOGY
JEROME SPAR, *Chairman* EDWIN L. FISHER, *Secretary*

SECTION OF MATHEMATICS AND ENGINEERING
PAUL HARTMAN, *Chairman* NICHOLAS V. FEODOROFF, *Secretary*

Past Presidents
WILLIAM K. GREGORY
VICTOR K. LAMER
HORACE W. STUNKARD
M. L. CROSSLEY
WALTER S. ROOT
HARDEN F. TAYLOR
M. L. TAINTER

The Sections and the Division hold meetings regularly, one evening each month, during the academic year, October to May, inclusive. All meetings are held at the building of The New York Academy of Sciences, 2 East Sixty-third Street, New York 21, New York.

Conferences are also held at irregular intervals at times announced by special programs.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
VOLUME 65, ART. 5 PAGES 357–652
April 11, 1957

Editor in Chief
OTTO V. ST. WHITELOCK

Associate Editor
FRANKLIN N. FURNESS

MERCURY AND ITS COMPOUNDS*

Conference Chairmen
CECIL V. KING, HARRY GOLD, AND HAROLD WOLFF

Consulting Editor
CECIL V. KING

CONTENTS

Foreword. *By* CECIL V. KING 359

Part I. Physics and Chemistry

Mercury: Its Scientific History and Its Role in Physical Chemistry and Electrochemistry. *By* CECIL V. KING 360

Purification of Mercury and Its Physical Properties. *By* CHARLES L. GORDON AND EDWARD WICHERS 369

The Growth of Mercury Crystals from the Vapor. *By* GERALD W. SEARS 388

The Physical Properties of Mercury Important in Electronics. *By* ERWIN F. LOWRY 417

Recent Studies in the Structural Inorganic Chemistry of Mercury. *By* WILLIAM N. LIPSCOMB 427

Oxymercuration of Alkenes. *By* GEORGE F WRIGHT 436

---

*This series of papers is the result of a conference on *Mercury and Its Compounds* held by The New York Academy of Sciences, Section of Physics and Chemistry and Section of Biology, April 6 and 7, 1956.

A Physicochemical Rationale for the Biological Activity of Mercury and Its Compounds. *By* Walter L. Hughes 454

Relationship between Chemical Structure and Biological Activity in Mercurial Compounds. *By* Harris L. Friedman 461

Discussion: Part I 471

Part II. Pharmacology and Toxicology

Toxic Effects of Vapors of Mercury and of Compounds of Mercury on Plants. *By* A. E. Hitchcock and P. W. Zimmerman 474

The Toxicology of Inorganic Mercury. *By* Leonard J. Goldwater 498

The Pharmacology of Mercury and Its Compounds. *By* Harold A. Shoemaker 504

An Analysis of the Excretory Products of a Mercurial Diuretic (Meralluride) by Column Chromatography. *By* John H. Moyer, Carroll A. Handley, and Richard A. Seibert 511

Renal Tolerance to Long-Term Administration of Organomercurial Diuretics. *By* William A. Leff and Harvey E. Nussbaum 520

Massive Doses of Mercurial Diuretics in Refractory Patients. *By* G. B. Gordon, I. Feder, and I. J. Greenblatt 538

Reactions to the Organomercurial Compounds. *By* Ethan Allan Brown 545

Discussion: Part II 553

Part III. Clinical Medicine

The Mode and Mechanism of Mercurial Diuresis in Normal Subjects and Edematous Cardiac Patients. *By* Raymond E. Weston 576

The Modification of Sodium-Retaining Effects of a Synthetic Steroid by a Mercurial Diuretic. *By* I. J. Greenblatt, G. B. Gordon, and I. Feder 601

Bioassay of Organomercurials. *By* Theodore H. Greiner 604

The Role of Maintenance Mercurials in the Management of Chronic Congestive Heart Failure: *By* John M. Evans 612

The Outpatient Management of the Cardiac Patient with Mercurial Diuretics. *By* William E. Lawrence and Margaret S. Klapper 619

Long-Term Oral Mercurial Diuretic Therapy in Congestive Heart Failure. *By* George C. Griffith and Edward M. Butt 623

Problems of Management of Congestive Heart Failure, with Special Reference to the Refractory Patient. *By* Emanuel Goldberger 628

Mercurial Diuretics in Pre-Eclampsia and Other Clinical Indications for the Use of Mercurials. *By* James W. Hendrick 633

Disccussion: Part III 640

Copyright, 1957, by The New York Academy of Sciences

FOREWORD

By Cecil V. King

New York University, New York, N. Y.

On April 6 and 7, 1956, The New York Academy of Sciences conducted a conference on *Mercury and Its Compounds*. The purpose was twofold. First, a panel of experts was gathered to present and discuss current research on mercury, whether it deals with the metal, its inorganic compounds, organic compounds of academic interest, or new mercurial drugs of interest in clinical applications. Second, this monograph was planned to record the findings and theories presented at the conference, and to give the authors an opportunity to add the review and background material so necessary to supplement brief oral presentation. It is hoped that the monograph will serve as a useful reference. Numerous articles concerning mercury and mercurials appear in the literature, but no comprehensive survey thereof has been published in recent years.

It is estimated that mercury and its compounds have more than 3000 uses. Obviously not all of them can be mentioned in a single small volume. Fortunately, the uses of any material can be directly correlated with its physical and chemical properties, and this is of tremendous aid with respect to mercury itself and to its inorganic compounds. The properties of complex organic molecules or, indeed, of any molecules in relation to their interactions with living matter are not so well defined or understood. Filling this gap in our knowledge suggests one goal of much of the research discussed in this volume.

Part I. Physics and Chemistry

MERCURY: ITS SCIENTIFIC HISTORY AND ITS ROLE IN PHYSICAL CHEMISTRY AND ELECTROCHEMISTRY

By Cecil V. King

Department of Chemistry, Washington Square College, New York University, New York, N. Y.

Historical Background

The noble metals were naturally the first to be discovered and utilized by the human race, since they are found in nature either in the free state or as easily decomposable compounds. Gold, silver, and mercury were known in prehistoric times. Tin, lead, and copper appeared at the beginning of written history, while iron and the more active metals have been utilized only in comparatively recent times. There are indications that mercury was known in the 15th or 16th century B. C. Mercury compounds are said to have been used as drugs in Greece by Hippocrates, the "Father of Medicine," at about 400 B. C., and in India and Persia at about the same time.

Mercury seems to have had few real uses in ancient times. It was used at an early date in extracting gold and silver from their ores by an amalgamation process similar to that used today. It was probably used as an "artificial horizon" by early astronomers, navigators, and surveyors. The metal was much discussed by philosophers in the days of Aristotle in the 4th century B. C., and many of them considered it a quality or essence rather than a material in its own right. It was to them the "prime material" of all metals, one that gave them their characteristic properties. The name quicksilver is indicative, for it was believed to be "living silver," the essence that imparted the luster and chemical inertness to silver. It should be possible, these people believed, to add it to other materials or to remove it from them, thus changing their properties.

To the more grubby alchemist, who had learned a little of this philosophy, mercury represented the hope of converting the base metals into silver, or gold, or something even more valuable. To all, mercury was a beautiful and valued plaything. Materials are admired or utilized because of some of their outstanding physical or chemical properties. The high density, mobility, luster, freedom from tarnish, high surface tension, and the ease with which this element wets, dissolves, or amalgamates with other metals made mercury seem most desirable. The fact that most of its alloys soon become dull and tarnished must have been disappointing. The alchemist's modern counterpart, the young student of chemistry, amalgamates his ring and watch with the contents of the demonstration barometer at the first opportunity. In a day or two he is looking anxiously for an easy way to remove the mercury.

The unique characteristics of mercury are not properties that could make it of great value to ancient peoples; indeed, some of its most useful properties are those that were unknown to them or could not be exploited until very recent years. In scientific work mercury acquired especial importance after suitable glass apparatus was developed. In 1643, Torricelli showed that mercury in a sealed, inverted tube always sank to a level of about 76 cm. Not long after this, Pascal, Boyle, and others showed that the level was lower on a mountain top. By 1662, Boyle was able to show convincingly that the mercury level was dependent on the outside air pressure, and thus that the weight of the column was equal to the weight of a similar column of air extending to the top of the earth's atmosphere. Now the way was open for the development of mercury barometers, manometers, and other instruments based on the same principles. No better method of measuring high pressures than the mercury manometer was devised for many years, and steel manometer tubes as high as 400 meters were erected for certain experiments. The weight of a column of mercury has been used ever since, directly or indirectly, as a standard of pressure.

In the early days of chemistry, gases were generated, and then confined in bladders of animal origin. With the development of glass apparatus some gases could be collected over water, others over mercury. The confinement of air and oxygen over mercury by K. W. Scheele, A. Lavoisier, and Joseph Priestley played an important part in elucidating the nature of air. Measurement of the volume, pressure, and temperature of gas samples and of the relative volumes of different gases involved in chemical reactions was of greatest importance in chemical theory, and it would have been almost impossible to perform some of the experiments without confining the gases over mercury.

A few ores contain free mercury, but most of the metal is found as cinnabar, the red sulfide HgS. The mines at Almadén, Spain, have produced cinnabar continuously for about 2500 years. In the halcyon days of ancient Rome, much powdered cinnabar was sent there from Almadén for direct use as a cosmetic. Cinnabar is still employed as a pigment (vermilion), but its use in cosmetics has declined, and such use is forbidden by law in the United States.

Many other deposits of mercury have been discovered throughout the world, but there is little hope of finding a plentiful and cheap supply of the metal. It is estimated that at the present rate of mining all known deposits will be exhausted within 100 years. The government of the United States began stockpiling mercury several years ago, banned its export, and established a "support" price for the metal. Actually the world price has gone well above this figure. It is rumored that mercury is important in the American atomic energy program, perhaps as a heat-transfer medium. This report has been neither confirmed nor denied.

Mercury vapor is poisonous, and the effects are cumulative. In the 17th century the miners of Almadén were granted the shortest working hours in the history of labor. This was not due to the generosity of the employer, the Spanish crown, but was an absolute necessity for the operation of the mines. Even with modern methods and careful health supervision, workers in mercury mines and smelters must have short working hours and long vacations. Spilled mercury in the laboratory or plant is difficult to recover completely. Fortunately, dirt and tarnish, while they do not change the vapor pressure, do impede evaporation, and powdered sulfur sprinkled about and worked into crevices is a further hindrance, since it coats the metal with HgS. Low concentrations of the vapor can be determined by drawing the air through paper impregnated with selenium sulfide (SeS_2), black mercuric sulfide resulting if vapor is present.

Some Present Uses of Mercury

The low vapor pressure of mercury (0.0013 mm. at 20° C.) is of great advantage in many of its applications. In certain types of high-vacuum work, even traces of the vapor must be eliminated, and mercury seals, manometers, McLeod gauges, and mercury-vapor diffusion pumps must be either isolated with multiple cold traps or gold-foil traps, or replaced with other equipment.

The low heat capacity of liquid mercury (0.033 cal./gm.), the comparatively high heat of vaporization (14.2 kcal./gm.-atom), and the reasonable range of vapor pressures at elevated temperatures have made possible the successful development of mercury-vapor turbines. The metal is easily heated to 500° C. by a coal-burning furnace and vaporized at a pressure of 8 or 9 atmospheres. After running a turbine, the condensing vapor is used to heat water in the conventional high-pressure steam range. The combination results in a considerable saving of fuel. Unfortunately, the initial cost of installation is high; if many large power plants of this kind were built, the price of mercury would skyrocket, since each would require several hundred thousand pounds of the metal. There are, naturally, special problems of corrosion, and hazards of leakage or explosion.

The welding together of 2 pieces of frozen mercury at $-78°$ C. by application of slight pressure depends on a property common to all metals, first explored by the German physical chemist-metallurgist G. Tammann nearly 40 years ago. Clean metals, in general, will sinter together when heated to temperatures greater than 0.6 of their melting points on the absolute scale. In the case of mercury, $-78°$ C. is about 0.8 of the absolute melting point. The same principle is the basis of "powder metallurgy"; metals difficult to fuse and cast often can be sintered together at workable temperatures.

The metal gallium melts at 29.7° C.; curiously, it is only slightly miscible with mercury. The problem of miscibility may be epitomized, as was done by the earliest chemists, in the Latin words *similia similibus solvuntur*—"like dissolves like." Water and the hydrocarbons, for example, are alike neither physically (dielectric constant, dipole moment) nor chemically (molecular groups and structure), and they are immiscible. While the differences between mercury and gallium are not as clear, it is evident that these differences lie in the nature of the interatomic attractive forces. The boiling point of gallium is 1960° C. above its melting point, which indicates that these forces are much stronger than they are in mercury.

Mercury and gallium have been used in making up a system of 8 immiscible liquid layers.[1a, 1b] The system may be shaken because no 2 phases are miscible. The 8 liquids are mercury, gallium, white phosphorus, perfluorodimethylcyclohexane, aniline, water, silicone oil, and paraffin oil.

Mercury, of course, is not miscible with methylene iodide but, with the aid of a protective colloid, one can create stable fluid emulsions of the 2 substances that have specific gravities in the range of from 3.5 to 7.5. These emulsions are useful for the rapid estimation of the specific gravity of solids. For example, a sample of cinnabar would sink in the densest emulsion mentioned. The emulsions were designed by Edgar Wagner, and may be bought in labeled sets.* They will remain stable for many years if the methylene iodide is not allowed to evaporate.

When mercury flows over glass there is some generation of frictional electricity. In a vacuum, the electronic excitation of atoms of the vapor gives rise to a faint greenish glow. This was first observed, no doubt, by someone carrying a barometer column in the dark. If a trace of neon is sealed with mercury in an otherwise evacuated tube, the characteristic neon glow appears when the tube is shaken. The ease of excitation of mercury vapor is an important factor in today's extensive and varied uses of the metal in the lighting and electronics industries.

Mercury has played an extremely important role in the development of modern electrochemical theory and practice; some of its uses and the properties that make them possible will be described below. In the earliest days of industrial electrochemistry, the fact that dilute amalgams of the alkali metals could be made and decomposed at will led to the development of the mercury-cathode cell for making the pure hydroxides. Essentially the same process is used on a very large scale today. In the ordinary electrolysis of brine the cathode solution cannot be freed entirely from chloride. With a mercury cathode, dilute sodium amalgam is produced, and this amalgam is continually drawn off and decomposed with water to give chloride-free sodium hydroxide.

If an aqueous ammonium salt is electrolyzed with a mercury cathode, ammonium amalgam is obtained. It is similar to other metal amalgams and appears to contain ammonium ions and free electrons; the radical NH_4 cannot be extracted nor isolated. The amalgam is quite stable when frozen at $-78°$ C., but above $-20°$ C.[2] decomposes rapidly into ammonia, hydrogen, and mercury. It can also be made by shaking sodium amalgam with an ammonium-salt solution, and at room temperature the amalgam immediately swells to 20 times its original volume as it decomposes. There is no commercial application for this phenomenon.

Mercury oxide is used in the Ruben dry cell[3a, 3b] and this compound is reduced to the pure metal in the cathodic reaction during discharge. The energy contribution to the cell is less than that of the anode reaction, but it aids greatly in such factors as the over-all efficiency, resistance to corrosion, lack of hydrogen swelling, and nonpolarization on high current drain.

The electrical resistivity of mercury is low, but is so precisely reproducible that it is used as an international standard. The metal is used in calibrating cells to serve as standards in measuring the conductance of electrolytic solutions. The metal's high conductance, mobility, and expansion factor make it possible to use mercury in temperature and pressure controls and in electrical switching devices of many types.

The use of mercury in the calomel-reference half-cell and in the Clark and Weston standard cells is well-known. Such cells are characterized by the stability and precise reproducibility of their potentials. The electrode processes are reversible, and small currents in either direction leave the metal and solution phases in unchanged equilibrium. The mercury-mercurous ion, cadmium-cadmium ion "exchange currents" are high, so that the electrodes do not remain polarized. Solid metals undergo such exchange in only a few surface atomic layers, and a portion of the exchange is irreversible. The mobility of mercury and the higher internal diffusion rate of its atoms, or of other atoms in the amalgams, are doubtless responsible for these desirable properties.

---

*Obtainable from R. P. Cargille Laboratories, Inc., New York, N. Y.

The lack of corrosion of the metals in the amalgams of the standard cells is another contributing factor.[4] This is due to the high hydrogen overvoltage on mercury. When a metal undergoes electrochemical corrosion, with separate anodic and cathodic areas, the measured potential is a mixed, or corrosion, potential that may vary with the rate of corrosion. It is difficult to keep a zinc surface clean, and in a zinc-salt solution it is likely to corrode slowly, with consequent drift and uncertainty of potential. Amalgamation prevents this and gives the same electromotive force (e.m.f.) as does pure zinc.[5]

It has been shown that only the (111) face of a single crystal of copper gives a stable potential when equilibrated with solutions of copper salt; polycrystalline copper is inhomogeneous in potential until surface rearrangement has taken place.[6] If the copper is amalgamated, the equilibrium potential is attained much more quickly.

The 2-phase amalgams are convenient, since the potentials of both phases are the same and are independent of total composition over a wide range. Since the relative amounts of the 2 phases are unimportant, it is not necessary to weigh the metals with extreme care.

Amalgams are used in obtaining the standard potentials of the alkali metals and the relative free energies of their ions.[5] These metals, of course, react vigorously with water, but the dilute amalgams are sufficiently nonreactive to allow measurement of their potentials against a suitable standard reference (such as a silver-silver chloride electrode in a chloride solution). In the method devised by G. N. Lewis,[5] the same amalgams are measured versus the pure metals in a nonreactive, nonaqueous solution of a salt of the metal—for example, in ethylamine. With proper experiments or a knowledge of the activity coefficients in the aqueous solutions, the standard potentials can be calculated.

The use of mercury in polarography[7] can be mentioned here only briefly. The dropping mercury electrode has various advantages over other metal electrodes: as the drops form, a clean surface is continually presented to the solution, and the high hydrogen and oxygen overvoltages allow a wide range of applied potentials for the study of both reduction and oxidation processes. The disadvantages are the increasing electrode area as the drops grow, the slow and irregular stirring, and the fact that no standard form of vigorous stirring can be used. Also, both the drop size and drop time change with the concentration of the solution and with the applied potential, since these changes alter the interfacial tension.

Most of the work in this field has been concerned with *rapid* electrode processes, and the measured currents include the limiting, diffusion-controlled values. This has been especially useful in analytical chemistry, since the diffusion current is proportional to the concentration of the reacting species, and the half-wave potential identifies it. Also, diffusion coefficients can be evaluated, and they are useful in other connections. In recent years more work has been done on *slow* electrode reactions, where no concentration gradients are set up, and there is no limiting diffusion-controlled current.[8, 9]

A limited amount of work has been done with dropping amalgam electrodes and with a dropping gallium electrode. Experiments have also been conducted with solid electrodes such as platinum, but they are subject to the disadvantage of an unknown and unreliable surface.

Many other experiments make use of electrically polarized mercury electrodes. In the absence of mercury ions, it is said that the metal approaches the "ideally polarizable" electrode: that is, there is little or no corrosion and only slight leakage of direct current across the mercury-solution interface at low applied potentials. The system is thus ideal for the measurement of electrical double-layer properties such as capacity and A.C. impedance.[10a, 10b] The fact that the interfacial tension of mercury in contact with an electrolytic solution changes with applied potential is the basis of the Lippmann capillary electrometer. This instrument was once a favorite null-point indicator for use with the potentiometer, and it was described in every textbook of physical chemistry or electrochemistry.[11] Since an extremely small quantity of electricity is needed to charge the double layer at a mercury-sulfuric acid interface in a fine capillary tube, the electrometer could be used in measuring the e.m.f. of high-resistance cells. It has now, of course, been replaced by sensitive galvanometers and electronic devices, but instruments based on the same principle are used in determining "electrocapillary curves."[12]

The change in interfacial tension with charge is the basis of an interesting demonstration sometimes called the "mercury heart." A small pool of mercury is placed in a large watch glass and covered with an electrolyte that lowers the interfacial tension, such as dilute sulfuric acid containing some dichromate. On touching the edge of the mercury with an iron wire, which acts as the anode in an electrical couple, the double layer is discharged, the interfacial tension increases, and the mercury contracts, breaking contact with the iron. The double layer now forms again, the pool spreads until it touches the wire, and the process repeats itself. With proper concentrations of solution, the motion is quite vigorous, and it results in a pulsating triangular or heart-shaped figure.

It was at one time thought necessary to establish a scale of "absolute" single electrode potentials for the thermodynamic treatment of electrical cells. It was also thought that the dropping mercury electrode could be adapted to this purpose. Ostwald, Paschen, Palmaer, Helmholtz, and others worked on this problem.[10a, 10b] In a dilute mercurous salt solution, drops of mercury from a capillary outlet carry adsorbed salt down with them until the concentration around the newly forming drops is such that no electrical double layer is set up and there is no potential drop across the interface. In principle, the potential of a cell composed of this electrode and a calomel half-cell is entirely due to the half-cell. In this way the decinormal KCl-calomel cell was assigned a potential of +0.572 volt versus a "null" electrode.

It was also believed that, when mercury is polarized to the point of highest surface tension, the electrocapillary maximum, there should be no potential drop across the interface. The polarized mercury should then contribute nothing to the potential when combined with a reference electrode. In practice, neither method is sufficiently reproducible to establish a null electrode with sufficient precision for a modern standard. It is now believed that, even though no potential drop exists across the mercury-solution interface, this may not apply to the outer diffuse part of the double layer.[12] In principle, any method of setting up "absolute" single-electrode potentials ignores the interdependence in an electrical cell of anode and cathode reactions; it likewise ignores the fact that the true seat of the e.m.f. lies in the points of inhomogeneity in the electrolyte between the electrodes and not in the solution-electrode interfaces or in the metal-metal contacts.[13]

Despite the obvious importance of knowing the exact amount of mercurous salt adsorbed on a mercury surface under various conditions, no satisfactory technique of making direct measurements has been devised. Mercury cannot be immersed in a solution containing a radiotracer, and then removed for measurement without disturbing the surface. Also, it is difficult to present a large area of mercury to a small volume of solution in order to measure the decrease in concentration of the latter. The use of drops of mercury seems logical, but how can they be removed with their adsorbed layer intact? Preliminary experiments along these lines have been carried out by von Euler and Zimmerlund.[14]

The true area of a mercury surface customarily is taken to be the same as the measured area, although this has been questioned with respect to examination on an atomic scale, and it evokes argument about the meaning of "true surface area." Nevertheless, the above assumption and the "ideal polarizability" of a mercury cathode form the basis of the famous Bowden-Rideal method of estimating true surface areas of metals[15] and its modern modifications.[16] In this method the mercury cathode, in a suitable electrolyte, is polarized with a small constant current until its potential versus a reference electrode has risen by a fixed amount, for example, 100 mv. Great care is taken to be sure that all of the current is used to build up a double layer, and that none of it is dissipated in the measuring instrument. The number of coulombs of charge per cm.^{2} is now known. On substituting another cathode, which must also be ideally polarizable under the same conditions, it is assumed that charging through the same potential range requires the same number of coulombs per cm.^{2} of true surface area. The Bowden-Rideal method often indicates larger areas than are indicated by other methods. Some metals may absorb atomic hydrogen and, in other cases, the double layer formed may not be entirely analogous to that on mercury.

Mercury is a noble metal, with a standard oxidation potential of -0.80 v.; hydrogen overvoltage on its surface is high; and, of course, it normally does not dissolve in dilute hydrochloric acid with the evolution of hydrogen. With suitable arrangement, anodic-cathodic self-polarization can be obtained on 2 portions of the same mercury sample with sufficient potential to cause evolution of hydrogen. The experiment was devised by S. W. J. Smith in 1909, and is described by U. R. Evans.[17] Part of the mercury is allowed to drop through dilute hydrochloric acid from a capillary tip, while another portion presents a stationary meniscus to the solution. The expanding drops do not come to equilibrium with the solution; they constitute the anode, while hydrogen is formed at the stationary part.

X-Ray Diffraction Studies of Mercury

The study of X-ray diffraction by liquids has contributed immensely to the knowledge of liquid structure and to the theory of solutions. While satisfactory diffraction patterns of many liquids can be obtained today, for obvious reasons mercury was the first liquid to be investigated in this manner.[18] Since mercury is monatomic, its diffraction patterns are simpler than those of many other liquids. These patterns show a considerable degree of short-range atomic order, the average interatomic distance of nearest neighbors in liquid mercury being similar to that in the solid state of the metal. There is, of course, no long-range order, as there is in crystals. The contribution to the theory of solutions is discussed by Hildebrand and Scott.[1]

Isotopes of Mercury

There are 7 naturally occurring isotopes of mercury. Two of these can be made from gold by nuclear reactions: Hg^{197} by bombardment with deuterons from an ion-accelerator (EQUATION 1); and Hg^{198} by exposure of gold to neutrons in a nuclear reactor (EQUATION 2).

$$Au^{197} + H^{2} \rightarrow Hg^{197} + 2n^{1} \tag{1}$$

$$Au^{197} + n^{1} \rightarrow Au^{198} \rightarrow Hg^{198} + e^{0} \tag{2}$$

The second reaction is of interest since the Hg^{198} can be distilled from the gold entirely free from the other isotopes, and has been obtained in this manner in marketable quantities. Hg^{198} has a very sharp spectral emission line at 5461Å., which will probably replace other standards of spectral frequency and, for certain purposes, other standards of length. Quartz lamps, each containing about 4.4 mg. of Hg^{198}, are available commercially.

It may be noted that mercury also can be transmuted into gold. This transmutation has no commercial application and seems to be of minor scientific importance at the moment.

Mercury Compounds

There are 2 mercury (II) sulfides that have the same composition as HgS, but they have different crystalline forms. The ores usually contain the red cinnabar but, in a few deposits there is found a black sulfide that has been called metacinnabarite. The black sulfide is nearly always formed in laboratory precipitations. The red sulfide is the form thermodynamically stable at room temperature; that is, it has the larger (negative) free energy of formation from the elements, by 600 cal./mol. Why, then, is the black sulfide so easily precipitated in the laboratory?

This phenomenon is a matter of spontaneous nucleation of the crystals under particular experimental conditions. HgS is extremely insoluble and, when hydrogen sulfide is led into a mercuric salt solution, there is initially a very high degree of supersaturation. In such circumstances it is not unusual for the metastable form of a precipitate to appear. Red HgS is precipitated from solutions that contain very low concentrations of free mercuric ion, as in the presence of a large excess of iodide or thiocyanate, which respectively form the complex ions $HgI_4^=$ and $Hg(SCN)_4^=$.

Certain mercurial compounds are toxic to some lower organisms, and they have been used extensively to discourage bacteria, molds and mildew, fungi, various insects, and the like. At one time, mercuric chloride was widely used as an antiseptic. Much effort has been exerted to correlate the toxic effects with such measurable properties of the compounds as solubility, degree of ionization, and the ability to form compounds with or to coagulate proteins, but generally without much success. The approach to much research with mercurials, as with other classes of chemicals, is necessarily phenomenological in nature. If a substance is effective for one purpose, one tries it for related purposes; if 1 compound is partially successful, one tries all of its derivatives and its related compounds. As an example, since some mercurials are good fungicides, it was found that phenylmercuric acetate is especially effective against certain fungus diseases of grass. This led to the accidental discovery that the same compound is far more toxic to that scourge of lawns, crab grass, than to the desirable grasses.[19] Other related mercurials, however, are ineffective in this direction, and the newer substitutes are potassium cyanate and sodium dimethyl arsonate, which are totally unrelated compounds. Such specificity of action is hardly explainable today in terms of molecular properties or structure.

References

1a. Hildebrand, J. H. & R. L. Scott. 1950. The Solubility of Non Electrolytes. Reinhold. New York, N. Y.
1b. Kittsley, S. L. & H. A. Goeden. 1950. J. Am. Chem. Soc. **72:** 4841.
2. Deyrup, A. J. 1934. J. Am. Chem. Soc. **56:** 2594.
3a. Ruben, S. 1947. Trans. Electrochem. Soc. **92:** 183.
3b. Friedman, M. & C. E. McCauley. 1947. Trans. Electrochem. Soc. **92:** 195.
4. Uhlig, H. H. 1954. Proc. Natl. Acad. Sci. **40:** 276.
5. MacInnes, D. A. 1939. The Principles of Electrochemistry. Reinhold. New York, N. Y.
6. Tragert, W. E. & W. D. Robertson. 1955. J. Electrochem. Soc. **102:** 86.
7. Kolthoff, I. M. & J. J. Lingane. 1952. Polarography. Interscience. New York, N. Y.
8. Delahay, P. 1954. New Instrumental Methods in Electrochemistry. Interscience. New York, N. Y.
9. Bockris, J. O'M. 1954. Modern Aspects of Electrochemistry. Academic Press. New York, N. Y.
10a. Grahame, D. C. 1947. Chem. Revs. **41:** 441, 496.
10b. Grahame, D. C. 1955. Ann. Rev. Phys. Chem. **6:** 337-358.
11. Lehfeldt, R. A. 1904. Electro Chemistry. Longmans, Green. London, England.
12. Kortüm, G. & J. O'M. Bockris. 1951. Textbook of Electrochemistry. Elsevier Publ. Co. Houston, Texas.
13. Brönsted, J. N. 1955. Principles and Problems in Energetics (trans. by R. P. Bell). Interscience. New York, N. Y.
14. von Euler, H. & G. Zimmerlund. 1921. Arkiv Kemi Mineral. Geol. **8**(14).
15. Bowden, F. P. & E. K. Rideal. 1928. Proc. Roy. Soc. (London). **A120:** 59, 80.
16. Hutcheon, A. T. & C. A. Winkler. 1949. Can. J. Research. **B27:** 353.
17. Evans, U. R. 1948. Metallic Corrosion, Passivity and Protection. : 198. Edward Arnold & Co. London, England.
18. Mencke, H. 1932. Physik. Z. **33:** 593.
19. DeFrance, J. A. 1948. Flower Grower. **35:** 528.

PURIFICATION OF MERCURY AND ITS PHYSICAL PROPERTIES

By Charles L. Gordon and Edward Wichers
National Bureau of Standards, Washington, D. C.

INTRODUCTION

Most of the physical uses of mercury depend on its unique combination of properties: low melting and boiling points and high chemical stability. This combination of properties also makes it one of the easiest of substances to prepare in a very high degree of purity. The purpose of this article is to review the principal procedures that have been used for purifying mercury, to select the modifications of these procedures that have been found most convenient and useful, to point out suitable criteria of purity of the metal, and to present a tabulation of values for most of its important physical properties.

THE PURIFICATION OF MERCURY

Several hundred articles or notes have been published dealing solely with the purification of mercury, and many more on various uses of mercury, with incidental notes on its purification. All these methods embody one or more of the techniques that are selected in the following discussion as typical of the diversity and ingenuity of those who have required "pure" mercury. After the mercury had been treated and was thought to be pure, various tests of its purity were made in some cases; in many instances, however, the purity has been implied only by a statement of the treatment used in the purification.

Mechanical

The separation of mercury from solid impurities, not in solution, is usually effected by some kind of filtration. Pliny's writings (trans. 1856) indicated that isolation of mercury by pressing it through leather was known to gold workers before the 1st century. This process was revealed by Biringuccio (1540) as having been a secret art. Laboratory apparatus for continuous operation by means of the filtering action of leather was designed by Pfaundler (1879). Other filtering materials that have been advocated from time to time are: slitted filter paper (Bohn, 1887); bamboo (Karsten, 1888); cloth of various kinds, such as muslin (Hildebrand, 1909) or silk (Patten and Mains, 1917); glass frits (Grossman, 1924; Cueilleron, 1944); and a compressed filter paper ring (Moore, 1932).

More recently the use of an "adhesion ring" (Nieman and Nieman, 1952) that separates the dirty surface from the clean surface of the mercury has been introduced. The dry scum can also be removed by picking it up with a sticky surface (Hayes, 1955).

Air Oxidation of Impurities

Simple preferential oxidation of the contaminating base metals dissolved in mercury has been used for its purification. Crafts (1887) used suction to draw air through the impure mercury in an inclined tube. Berzelius and earlier workers observed the separation from mercury of the oxides of the metals by agitation with air (Maumené, 1887; Branchi, 1818). Later improvements and innovations relate to the technique or apparatus used. For gross impurities, Forbes (1912) used air oxidation and shaking with oxygenated charcoal powder. Margot (1914) heated the metal during oxidation to improve the separation. Harries and Evers (1921) compared acid extraction with air oxidation for the separation of lead and zinc from mercury. For lead they reported that 2 pours of mercury through nitric acid (sp. gr. 1.175) in their apparatus freed the mercury of lead, as did 8 hours with air agitation. The losses of mercury were, respectively, 3.8 and 2 per cent.

Chemical Oxidation of Impurities in Solution

Millon (1846) stated that mercury may be perfectly purified by agitating it with weak nitric acid. After washing the mercury with water, he dissolved most of the mercury in boiling pure nitric acid. The mercurous nitrate formed in this operation was reduced by heat to the oxide and then to the metal. Meyer (1863) dissolved the base metals from the impure mercury by allowing a stream of fine drops of the metal to fall through nitric acid. Other reagents that have been used include sulfuric acid (Branchi, 1818); ferric chloride solution (Wild, 1871); nitric acid solutions (25 per cent, Prausnitz, 1921; 5 per cent Dittmer and Gustavson, 1940); nitric acid with mercurous nitrate (Wolff and Waters, 1907); potassium permanganate (acidified, Russell and Evans, 1925; neutral, Dobrowsky, 1940; alkaline, Cueilleron *et al.*, 1949); potassium hydroxide (Cowsik, 1934); sodium hydroxide (Condit, 1955; Hailstone, 1913); potassium bichromate slightly acid (Brühl, 1879); and a 2 per cent solution of potassium cyanide with added sodium peroxide (Bettel, 1908). Bettel claimed removal of gold by this procedure.

Various kinds of apparatus and dispersers have been used for acid washing. Meyer (1863) used a drawn-out tip from a funnel to make the mercury fall in a fine stream into nitric acid. An all-glass version of this apparatus, as used in our laboratory prior to adoption of the air-bubbling technique described later, is shown in FIGURE 1. Karsten (1888) used a section of bamboo to hold back the gross dirt and to spray the mercury into the column of dilute acid. Gooch (1892) used a series of funnels with stems bent to form traps and with the tips drawn down to hold the acid and the wash water. After the mercury was atomized in a fine spray into a dilute nitric acid solution, it passed through the wash water to a collecting jar. A grooved glass joint was used as a disperser by Palmaer (1899). Muslin cloth was used as a disperser by Hildebrand (1909), and silk by Loomis and Acree (1911) and by Morse, Holland, and Carpenter (1911). The glass frit disperser was used by Dittmer and Gustavson (1940).

Because the extraction of impurities per pass of the mercury through the Meyer-type column was not very rapid, Morse, Holland, and Carpenter (1911) passed the mercury *1000 times* through the solution of nitric acid and mercurous nitrate. To make such recycling automatic, Desha (1909) added an air lift operated by suction to return the mercury to the top of the column. A re-circulating spray system, operated by air under pressure, was devised by Holmes (1946).

Another method of spraying mercury into the wash liquor is to operate a mercury lift inside the liquid by use of air pressure (or suction) through a U-tube that has an orifice in the bottom of the U-tube bend. Mercury entering through the hole is blown out through the nozzle into the wash liquid (Dixon and McKee, 1923).

The simple method for agitating mercury in contact with the acid in a suction flask by drawing air through the mercury is less troublesome than repetitive pouring of the mercury through a column. FIGURE 2 shows two 4-liter heavy-walled suction flasks connected in series to a water aspirator. A trap should be interposed to catch the acid spray and any droplets of mercury that accompany it. At the National Bureau of Standards a dilution of 1 part concentrated nitric acid (sp. gr. 1.42) with 9 parts water is used, and the acid washing is continued for 12 to 16 hours. The acid layer is then drawn off, and the operation is repeated with fresh acid. The metal is freed from the acid by washing with distilled water several times in the same way, using shorter periods. Dissolved mercury is recovered from the nitric acid solutions by electrolysis.

Mercury contaminated by sulfides is not readily purified by distillation,

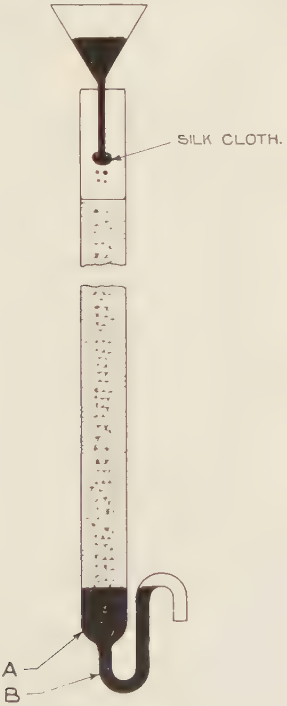


FIGURE 1. Modified form of Meyer column. *A*, processed mercury; *B*, outlet trap.

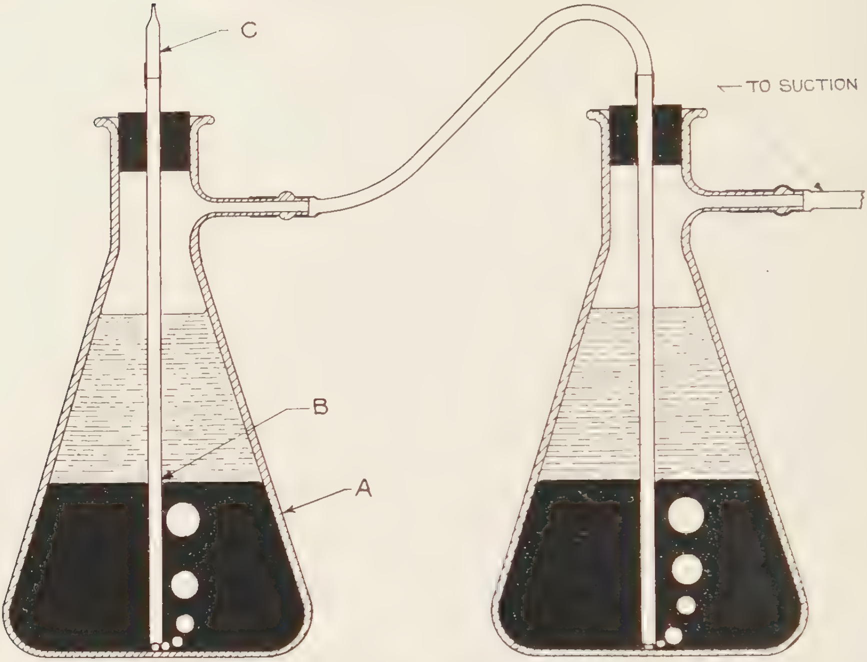


FIGURE 2. Apparatus for washing mercury with air agitation. *A*, suction flask; *B*, air inlet tube; *C*, metering orifice (to adjust air flow).

but it has been found to be easily purified by treatment with an acidified solution of hydrogen peroxide.

Distillation

Ordinary. Plain pottery retorts have been used for the distillation of mercury for centuries. Simple distillation is still recommended when excessive impurities are encountered. A cast-iron retort or one made from iron pipe (Wailes, 1930), with the outlet tube immersed in water, can be used. If the outlet tube becomes plugged with charred material during operation, such a retort may blow its gasket and release dangerous amounts of mercury vapor into the air.

With distillation at atmospheric pressure, impurities such as zinc and lead lower the volatilization rate of the distilling mercury (Millon, 1846). To overcome this difficulty the oxidizable base metals can first be chemically removed.

Vacuum (self evacuated). Slow distillation has been noted in barometers at ordinary temperatures (Hallock, 1888). The simplest type of vacuum still is an *inverted* U-tube, filled sufficiently high with mercury to have a Torricellian vacuum in the bent portion. Heat applied to the mercury in one leg distills it over to the other. The heat can be applied in several ways, for example, by a gas burner, as shown in FIGURE 3 (Weber, 1879), or an electric heater (Dunoyer, 1912). Making the receiving column a Sprengel pump serves to complete and maintain the vacuum. Thus Nebel (1887) improved the Weber still and Karsten (1888) simplified the Weinhold (1873) still. An alternative to producing the vacuum by *inverting* the still is to have a movable mercury reservoir that can be elevated and thus fill the still and the receiving column (Clark, 1883). The receiving column acts as a Sprengel pump, or has stopcocks at the top and bottom of the still that can be closed when the air is all displaced (Nayar, Rao, and Dasannacharya, 1933).

Vacuum (evacuated by external pump). Weinhold (1873) used a concentric-tube still of elaborate design with an attached Sprengel pump to create the starting vacuum in the system. A thermoregulator was provided to control the heat input. The still was of excessive height because of the necessity for placing the evacuating connection below the reservoir for the undistilled mercury, as can be seen from FIGURE 4. The vacuum was maintained by barometric columns in all the tubes opening to the atmosphere. Wright (1881) used a still similar to Weber's, but with a side tube to connect to a vacuum pump. This tube was sealed off when the vacuum was established. The addition of a water-cooled condenser is a logical step, and Wetzel (1909) utilized a cold finger over the central condenser column of the Karsten-type still. The use of silica glass was adopted by Hostetter and Sosman (1918) because their ordinary glass still collapsed when it overheated. Their design was the basis

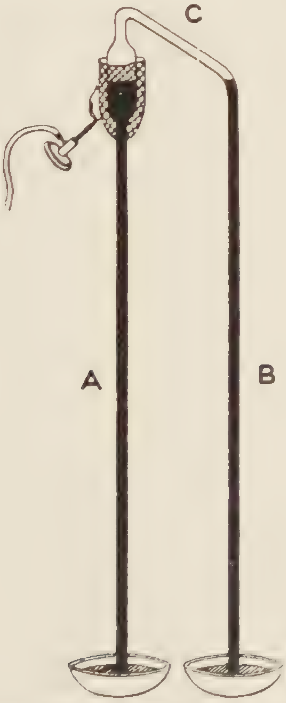


FIGURE 3. Inverted U tube still (Weber, 1879). A, impure mercury; B, distilled mercury; C, vacuum head.

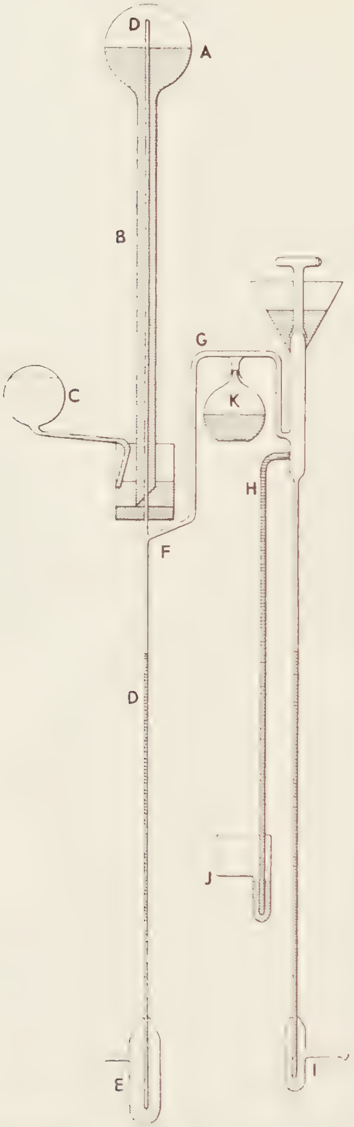


FIGURE 4. Vacuum still (Weinhold, 1873) with attached Sprengel type pump: *A*, boiling sphere; *B*, tube (length equivalent to highest barometric height); *C*, storage bulb; *D*, condenser tube (at least 20 cm. longer than twice highest barometric height); *E*, glass trap with side tube; *F*, *G*, vacuum connection; *H*, tube for siphon for modified Sprengel pump (slightly longer than barometric height); *I*, glass trap with side tube; *J*, reservoir for siphon; *K*, sulfuric acid container (for drying the vapor remaining in the apparatus).

of the still, shown in FIGURE 5, that has been used for the vacuum distillations carried out at the National Bureau of Standards for over 35 years.

Guards against contamination by spray from bumping have been introduced in several forms, such as a Vigreux-type trap (Goux, 1953) or a Kjeldahl-type trap (Vogels, 1934). Vogels also incorporated a counterbalanced cut-off system to turn off the electric heater. This system did not use contacts in the mercury itself, and opened the circuit if the internal pressure fell or if the amount of impure mercury in the reservoir dropped below a preset weight.

Hackspill and Sigot (1926) used an inner tube extending up into the still pot to just below the barometric height. This tube formed a part of the electric circuit that would turn off the still if the barometric pressure dropped.

The condensing chamber has been shaped variously from a simple bent tube to an alembic type. Thus Smith (1890) changed the design of Dunstan and Dymond (1890) to increase the condensing surface by means of an alembic-shaped still-head; Robeson (1929) effected a further improvement by providing a trap to prevent carry-over by spray.

Multiple distilling units (Hickman, 1929), some of which even include capacitance control (Milazzo, 1955), have been designed.

The method of heating the mercury has ranged from a simple gas burner through ring burners and electrical heaters to induction heating (Eberbach Corp., 1956).

Air flowing under reduced pressure. Hulett (1900) introduced the well-known method of preventing bumping by allowing gas or vapor to go up through the liquid in the still. Air or nitrogen was used at that time. Later, Hulett and Minchin (1905) recognized further advantages of air introduced in this manner when they compared the purification of solutions of zinc in mercury by the Weinhold still with their own apparatus. The Weinhold still automatically removes all residual air. Comparison of the two stills thus allowed comparison of distillation without oxygen and distillation in the presence of oxygen. With zinc amalgams, the vacuum distillation always yielded a product of approximately 1 part zinc per million parts of mercury whereas, on distillation with air at low pressure, the product was free of zinc.

In preparing amalgams for electrochemical studies, Richards and Wilson (1909) purified their mercury by means of a still similar to that of Hulett. Because they feared that the product of the distillation in air might contain a trace of dissolved oxygen, they used hydrogen instead of air. Hulett (1911) pointed out that this destroyed the main advantage of his form of still.

Duschak and Spencer (1917) modified the design of the Weinhold still by inserting a smaller tube through the center or condensing tube and bending back the upper end to dip under the mercury. Air was then bubbled through the distilling mercury.

The Hulett-type still used in mercury purification at the National Bureau of Standards is shown in FIGURE 6. This is modified from the original design of Hulett and includes an extra barometric column for an electrical cut-off in case of suction failure.

Arc stills. Knipp (1906, 1911) described a new form of mercury still in

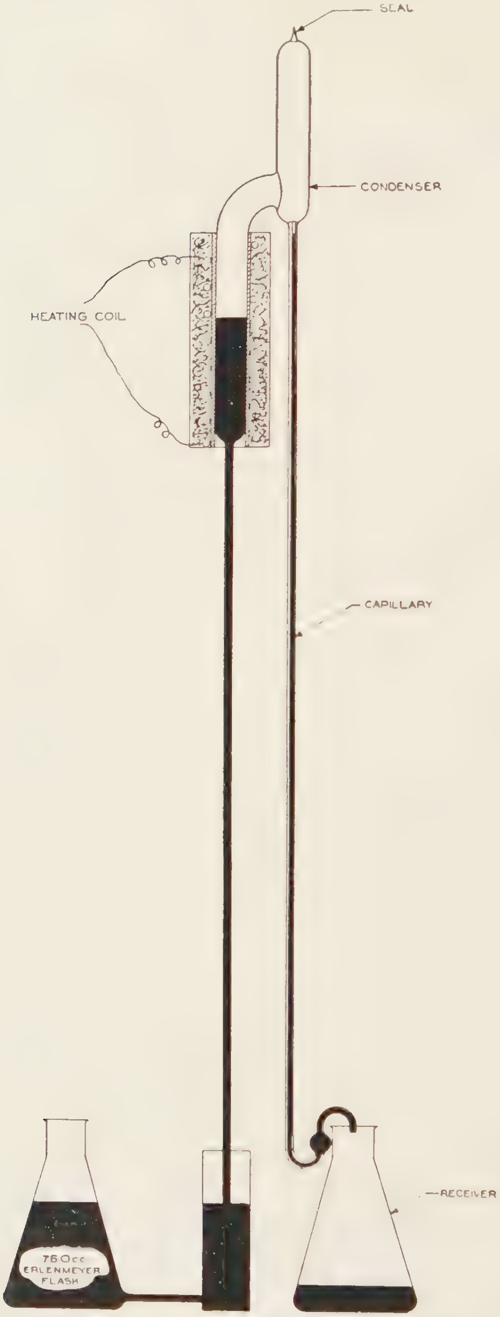


Figure 5. Electrically heated vacuum mercury still.

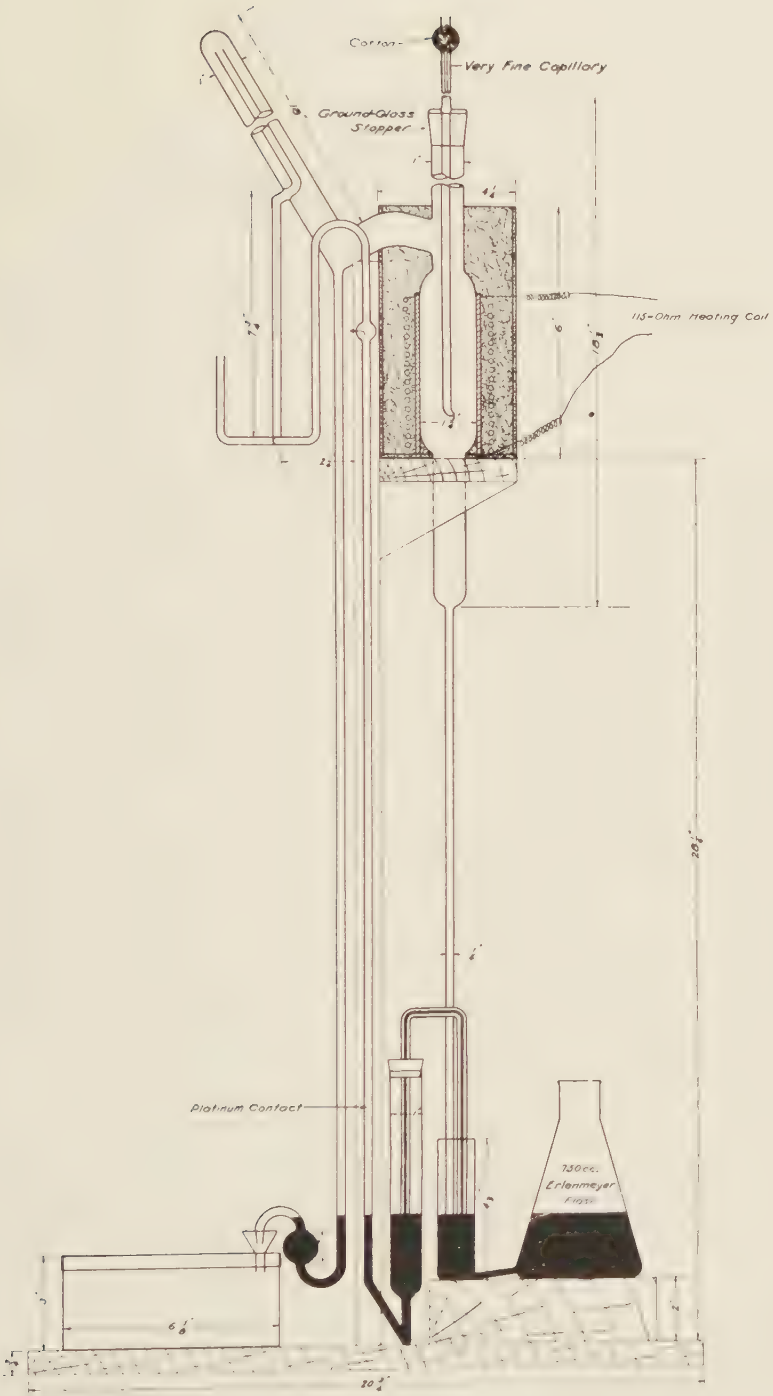


FIGURE 6. Modified Hulett mercury still.

which he added a condenser to a mercury vapor lamp. Waran (1926) devised a self-evacuating arc still. This still was improved by Sivaramakrishnan (1929) by an arrangement that utilizes the vapor from both limbs of the arc. Cowsik (1934) studied the removal of metals from mercury by the arc still and compared the purity of the mercury from ordinary vacuum distillation with that of the output from arc distillation. Both distillations carried over a fair amount of cadmium, zinc, and lead, but arc distillation also carried over copper and silver. Cowsik explained the difference in terms of sputtering rates (Au, 100; Ag, 67.1; Sn, 57.5; Ni, 8.5; Mo, 4.9; Al, 0.4; and Mg, 0). Because the sputtering rates of gold and silver are high, these metals are easily carried over in the arc still.

Electrolytic Purification

Electrolysis of the mercury from solution. Hannay (1873) studied the conditions for the electrolytic precipitation of mercury. Further studies were made by Clarke (1878), Smith and Frankel (1889), and others. This technique was applied to the problem of purification of mercury by Jaeger (1892), who used a nitrate solution and electrolyzed the mercury from a submerged dish of impure mercury into a second submerged dish. Improved forms of apparatus, including the introduction of mercurous perchlorate as the electrolyte, have been devised by Newbery (1929) and Newbery and Naude (1934).

In the National Bureau of Standards, electrolysis is used only for the recovery of mercury from the solutions produced by acid washing of the mercury. This recovery is easily accomplished by immersing two platinum wires in the acid solution and applying to them the output of an ordinary battery charger.

Electrolysis of impurities from the mercury. A number of workers have recommended various methods for aiding the removal of impurities by application of a potential between the mercury and the solution. Johnson (1901) found that low current, long electrolysis, and several changes of solution gave the best purification. This method has no advantage over simple acid washing.

Electrolytic action as an aid to purification has been combined with several of the other methods. Loomis and Acree (1911), among others, applied a potential between the forming drops and the acid of the Meyer column. Hanke and Johnson (1933) used a series of electrolyses alone with various solutions.

Drying

After treatment by solutions the mercury is usually washed and dried before distillation or use. A quick method for removing small amounts of water is the use of filter paper "sticks" to blot the mercury surface (Dougherty, 1943). Moore (1932) employed a heated tower packed with glass beads. He sprayed the mercury down the tower and through the beads in a manner similar to that used in the Meyer column. Carlson and Borchardt (1938) dried the acid-washed mercury in an inclined-tube drier by drawing heated air through it as in Crafts' air oxidation purifier. The method used by the National Bureau of Standards and by most other laboratories is to heat the mercury, usually in a porcelain dish, on a hot plate in a hood.

Storage

While an excessive number of papers have dealt with the subject of purification, very little has been published on the storage of purified mercury. Isaacs (1932) pointed out that the unsatisfactory appearance of four samples of mercury obtained commercially was probably related to the type of container. These samples came in three types of container: (1) wood; (2) stoneware jars; and (3) glass bottles with paraffin-covered cork stoppers that came in contact with the mercury. Both the wood and stoneware containers are difficult to clean and it is impossible to determine their state of cleanliness.

Experience at the National Bureau of Standards has shown that soft-glass bottles, scrubbed, thoroughly washed, and dried by baking, are best suited for the storage of mercury. When acid cleaning of containers is necessary, nitric acid is preferable to the commonly used chromic-acid cleaning bath. The bottles seem to become even better for the purpose with long continued re-use. A cork stopper, protected by parchment paper, and an inverted beaker covering the stopper and top of the bottle effect the best closure.

Complete Purification

Different methods of purification remove the metal impurities preferentially in different orders. Cowsik (1934) summarized these in a table that is the basis of the accompanying TABLE 1. It is apparent that the noble metals are

TABLE 1
REMOVAL OF METALS FROM MERCURY BY DIFFERENT METHODS IN DESCENDING ORDER OF EASE OF REMOVAL

Order of absorption of oxygen by amalgams (a)	Metals removed by KOH (b)	Order of removal by HNO_3 (b)	Order in vacuum distillation (b)	Order in arc distillation (b)	Order in 1 *N* H_2SO_4 (c)	Order in acid $KMnO_4$ (d)	Order in potential series (e)
Na	Sn	Mg	Au	Mg	Zn	Zn	Na
Mg	Zn	Al	Pt	Al	Cd	Cd	Mg
Zn	Pb	Cr	Ag	Ni	Tl	Mn	Al
Cd		Mn	Cu	Cu	Cu	Tl	Mn
Pb		Cd	Sn	Sn	Fe	Sn	Zn
Sn		Ni	Pb	Pt	Co	Pb	Cr
Tl		Sn	Zn	Ag	Ni	Bi	Fe
		Pb	Cd	Au		Cu	Cd
		Cu				Cr	Tl
						Fe	Co
						Mo	Ni
						Co	Sn
						Hg	Pb
						Ni	H
						W	Cu
							Hg
							Ag
							Pt
							Au

(*a*) Christiansen, 1897
(*b*) Cowsik, 1934
(*c*) Coriou, Huré, and Meunier, 1953
(*d*) Russell, 1929
(*e*) Latimer, 1940

most easily removed by vacuum distillation and that the base metals are removed by any of the other methods in somewhat the same order as that of their oxidation-reduction potentials. For the complete purification of mercury, therefore, a combination of methods is necessary if both noble and base metals are present. All recently proposed procedures include acid washing of the mercury followed by drying and distillation.

In this laboratory the routine is as follows: (1) filter very dirty mercury through a fritted funnel; (2) acid wash two times, as described previously, with air agitation (FIGURE 2); (3) wash with distilled water; (4) dry in porcelain dish on hot plate (if the surface criterion, as described below, indicates that the mercury is impure in respect to base metals, repeat steps 1 to 4 until criterion of purity is met); (5) filter through a glass frit; (6) distill with air under reduced pressure in apparatus previously described (FIGURE 6); (7) filter through perforated filter paper into reservoir of vacuum still; (8) distill under vacuum, as described previously (FIGURE 5); (9) store in clean bottles with filter-paper-covered stoppers.

CRITERIA OF PURITY

Base Metals

In the preparation of pure substances it is generally easier to perform the purification than to establish the degree of purity obtained. This has been notably true of mercury. Branchi (1818) noted that lead and bismuth in mercury caused the mercury to leave a black tail on porcelain; to determine impurities, he distilled off the mercury. Meier (1852) said that the tail consisted of the amalgamated foreign metals with adherent mercury. For a long time the appearance of the *surface* of the cleaned, dry mercury has been used as a qualitative indication of its purity, but a quantitative correlation was apparently not made until Isaacs (1932) showed that after preparation of separate samples of mercury containing 0.001 per cent each of copper, zinc, tin, lead, bismuth, cadmium, arsenic, and antimony, the samples at once lost the characteristic appearance of mercury and a film or "skin" formed on the surface. Silver and gold did not affect the appearance. Wichers (1942) reported that F. W. Schwab in 1935 found that a changed appearance of the surface of the mercury was discernible with even less contamination. The limiting sensitivity per 100 million parts of mercury was given as: 6 to 9 parts of Zn, 9 parts of Cu, 18 parts of Pb, 15 parts of Sn, and 14 parts of Sb. From this it is seen that the surface appearance serves as a most sensitive test for metals more base than mercury, but it does not indicate the nature of the impurity. Chemical and spectrochemical methods, which have often been used, are far less sensitive except when applied to concentrates obtained in some process of purification (as an example of this technique see Ewing *et al.*, 1955).

Müller (1942) found that a useful test for purity was the formation on mercury of a fairly stable foam that disappeared gradually, in 5 to 15 seconds, when mercury was shaken with distilled water.

Electromotive force measurements have been used by Hulett (Hulett, 1900; Hulett and Minchin, 1905) to determine the purity, or rather the limit of impurity, with respect to zinc. He used the e.m.f. of a cell: Hg, impure electrolyte (1 molar KCl + HgCl saturated) Hg, pure. Hildebrand (1909) and Patten and Mains (1917) were not successful in using this test.

In conducting a purification process an assumption that is often useful in the absence of more positive criteria of purification is that the separation characteristic of the operation at impurity levels that can be measured remains effective when the operation is repeated at progressively lower concentrations of impurity. This assumption has been confirmed in experiments on the removal of base metals from mercury by extraction with nitric acid. Special means were used to detect the presence of the base metals in very low concentrations. This was accomplished by adding to mercury, purified by our conventional methods, radioactive forms of zinc, copper, and cobalt. The concentration of these metals left in the mercury after successive periods of acid washing was determined by measuring the radioactivity of the metal. In this way it was found that the extraction process will remove zinc to levels below 1 in 10^{11}, copper to 1 in 10^{12}, and cobalt to 1 in 10^{10}—in each case the limiting sensitivity of the method used. It was also found that the rate of removal was in the following order: zinc, copper, cobalt. The important conclusion to be drawn from this work is that, when the progress of the nitric-acid extraction is observed using the simple appearance test to its limiting sensitivity of about 1 in 10^7, continuation of the extraction for specified periods can be relied upon to lower the residual concentration of the base-metal impurities to almost any desired value, and certainly to those observed in the experiments cited.

Further evidence of the extent to which base metals can be removed by washing with nitric acid could be deduced from the nature of the residue found in the boilers of the two stills used in our laboratory when they were dismantled for cleaning after an estimated 8000 kg. mercury had passed through them. The mercury remaining in the reservoir was bright and metallic in appearance after filtering. It contained 14 gm. silver and 0.56 gm. gold, but gave no visible evidence of any base-metal oxides.

It should be added that the appearance of a slight film on mercury after *prolonged* exposure to air does not necessarily indicate the presence of base metals. In our experience, every bottle of purified mercury will show, after some weeks or months, some evidence of surface impurities and, usually, a slight ring on the glass at the mercury surface. It is not known whether this is the result of slight oxidation of the mercury itself, promoted by contact with certain types of glass or by moisture in the air, or whether it is foreign matter sloughed off from the glass, or dust settling from the air. These films are so slight as to defy chemical examination. They can be removed by filtration and are not significant if they do not reappear promptly.

Noble Metals

The appearance test does not disclose the presence of metals such as gold and silver. Careful analysis is necessary to show the presence of small amounts of these metals, a fact demonstrated by the flurry of excitement caused by reports of the transmutation of mercury into gold under the influence of an

TABLE 2

PHYSICAL PROPERTIES OF MERCURY

Accommodation coefficient, a	1.00 ($-30°$ C. to $60°$ C.)
Angle of contact	128° (18° C.)
Atomic distance	3.005 Å.
number	80
volume	14.81 cc./gm. atom
weight	200.61
Boiling point	356.9° C.
Boiling point rise with pressure	0.0746° C. per mm.
Compressibility	4×10^{-6} cc. at 20° C. from 99 to 493 atm.
Condensation, temperature of	$-130°$ to $-140°$ C. on glass *in vacuo* (Seddig and Haase, 1949)
Conductivity	0.022 cal./sec. cm.^{3} °C. (variation with temperature—Hulm, 1950)
Critical density	3.56 gm./cc. (Lewis, 1953)
pressure	732.0 atm.
temperature	1677° C.
Crystal system	rhombohedral
Density	13.546 gm./cc. at 20° C. 14.43 gm./cc. at m.p. 13.595 gm./cc. at 0° C. (Batuecas and Fernandez Alonso, 1948)
Diffusion of vapor	0.1124 cm.^{2}/sec.
Diffusion of metals in mercury D (cm.^{2}/sec.) $\times 10^5$	
Lithium	0.9
Sodium	0.9
Potassium	0.7
Rubidium	0.5
Cesium	0.6
Calcium	0.6
Strontium	0.5
Barium	0.6
Copper	1.06 (Cooper and Furman, 1952)
Silver	1.1
Gold	0.7
Zinc	1.57 (Stromberg, 1952)
Cadmium	2.07 (Stromberg, 1952)
Mercury	0.007
Thallium	1.03 (Cooper and Furman, 1952)
Tin	1.68 (Cooper and Furman, 1952)
Lead	1.16 (Cooper and Furman, 1952)
Bismuth	0.99 (Cooper and Furman, 1952)
Electrochemical equivalent	1.0394 mg./coulomb (univalent) 2.0788 mg./coulomb (divalent)
Electrode potentials, normal	
$Hg^{++} + 2e^- = Hg$	0.85 v.
$Hg_2^{++} + 2e^- = 2Hg$	0.79 v.
$2\ Hg^{++} + 2e^- = Hg_2^{++}$	0.92 v.
E.m.f., thermal, rel. to Pt—cold junction, 0° C; hot, 100° C.	-0.60 mv. (American Inst. of Physics, 1941)
Enthalpy	6.942 abs. joules/gm. at 50° C. (Douglas *et al.*, 1951)
Entropy S_l	18.19 cal. deg.$^{-1}$ mol^{-1} (25° C.) (Busey and Giauque, 1953)
S_g	76.2 cal. deg.$^{-1}$ mol^{-1} (25° C.)
Expansion coeff. of liq.	182×10^{-6} cc. (20° C.)
Freezing temperature	$-38.87°$ C. (Chino, 1949)
Heat capacity	0.0334 cal./gm. at 20° C. (Busey and Giauque, 1953)

TABLE 2—*Continued*

Heat of fusion	2.7 cal./gm.	
Hydrogen overvoltage	1.06 v. (Post and Hiskey, 1950)	
Ionization potentials	10.43 v.	1st electron
	18.75	2nd
	34.3	3rd
	(72)	4th
	(82)	5th

Isotopes of mercury

Mass. No.	*Half life*	
189	20 min.	Au^{197} (p,9n)
191	55 min.	Au^{197} (p,7n)
192	5.7 hr.	Au^{197} (p,6n)
193	10 hr.	Au^{197} (p,5n)
194	0.40 sec.	Au^{197} (p,4n), Hg(p,)
195	40 hr.	Au^{197} (p,3n), Au(d,4n)
196	0.16%	
197	65 hr. [24 hr.]	Au^{197} (d,2n) [Au^{197} (p,n)]
198	10.02% [2.3×10^{-11} sec.]	[Hg^{198} (γ,γ)]
199	16.92% [42 min.]	[Hg(n,n)]
200	23.10%	[Hg^{199} (n,γ)]
201	13.22%	
202	29.72% [2.4×10^{-11} sec.]	[Hg^{202} (γ,γ)]
203	43.5 days	
204	6.84%	
205	5.5 min.	

(National Bureau of Standards, 1950–1952; Atomic Energy Commission, 1952–1955)

Magnetic moment Hg^{199}	+0.4993 nuclear magnetons (Proctor and Yu, 1949)
Magnetic susceptibility	-0.15×10^{-6} C.G.S. (18° C.)
Potential, contact Hg/Sb	−0.26 v.
Hg/Zn	+0.17 v.
Pressure, internal	13.05 atm.
Reflectivity	71.2% at 550 mμ
Refractive index	1.6 to 1.9 at 20° C.
Resistance, pressure effect on	cf. Bridgman, 1952
temperature coeff. of	0.9×10^{-3} at 20° C.
Resistivity	95.8×10^{-6} ohm/cm. at 20° C.
Solubility of mercury in water	20–30γ/liter (Pariaud and Archinard, 1952)
Solubility of metals in mercury	cf. TABLE 3
Specific heat	0.033 cal. gm. °C.
Surface tension	480 dynes/cm. at 0° C.
affected by adsorbed gases	(Foryst, 1951)
temperature coefficient	−0.19 d/cm./°C. (Pugachevich, 1947)
Vapor pressure	see figure 7
at 40° C. to 240° C.	cf. Dauphinee, 1951
at 250° C. to 360° C.	cf. Spedding and Dye, 1955
Vaporization, heat of	14.67 cal./gm. atom (25° C.)
Viscosity (liq.)	0.0155 poise (20° C.)

electric discharge (Miethe, 1924). In actual fact, the mercury already contained the gold. Riesenfeld and Haase (1925, 1926), Haber *et al.* (1926), Tiede *et al.* (1926), and others showed that a very small amount of residual gold in purified mercury remained even after 2 or more fractionations under reduced pressure.

TABLE 3

SOLUBILITY IN MERCURY AT 18° C. (PER CENT BY WEIGHT)

0Li .09 (a)													
Na 0.68 (a)	Mg 0.24 (a)												
K 0.80 (a)	Ca 0.30 (a)	Ti $<1 \times 10^{-5}$ (b)	V $<5 \times 10^{-5}$ (b)	Cr $<4.10^{-7}$ (c)	Mn 1.7×10^{-7} (c)	Fe 1.5×10^{-6} (c)	Co $<1 \times 10^{-6}$ (c)	Ni $<2 \times 10^{-6}$ (c)	Cu 2×10^{-3} (b)	Zn 2.15 (a)	Ga 1.3 (d)(35°)		
Rb 1.54 (a)				Mo $<2 \times 10^{-5}$ (b)					Ag 0.042 (a)(g)	Cd 4.92	In 27.0 (f)(25°)	Sn 0.62 (a)	Sb 2.9×10^{-5} (a)
Cs 4.34 (a)	Ba 0.33 (a)			W $<1 \times 10^{-5}$ (b)					Au 0.13 (a–h)		Ti 42.8 (a)	Pb 1.3 (a)	Bi 1.4 (a)

(a) Tammann and Hinnüber, 1927
(b) Irvin and Russell, 1932
(c) deWet and Haul, 1954
(d) Spicer and Bartholomay, 1951
(e) Liebhafsky, 1949
(f) Spicer and Banick, 1953
(g) Sunier and Hess, 1928
(h) Sunier and White, 1930

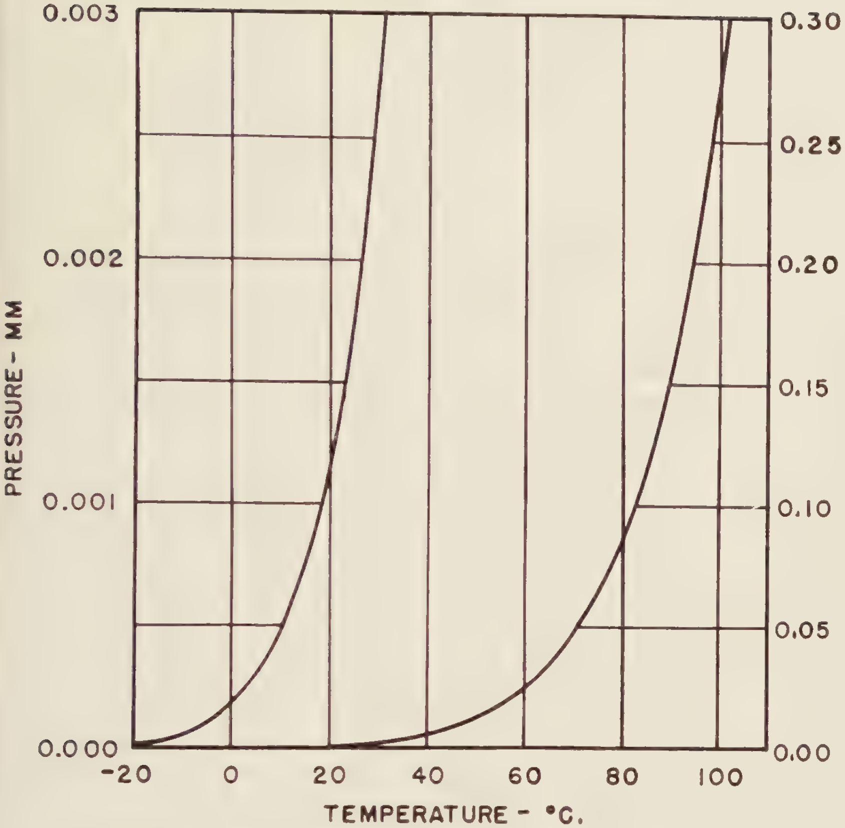


FIGURE 7. Vapor pressure curve of mercury (pressure in mm. of mercury).

PHYSICAL PROPERTIES OF MERCURY

Unless otherwise indicated, the references for most of the data given in TABLE 2 may be found in the corresponding sections of the International Critical Tables (National Research Council, Washington, D. C., 1926).

References

AMERICAN INSTITUTE OF PHYSICS. 1941. Temperature, Its Measurement and Control in Science and Industry. Reinhold. New York, N. Y.

ATOMIC ENERGY COMMISSION. 1952-5. Nuclear Science Abstracts. **6-9.**

BATUECAS, T. & J. I. FERNANDEZ ALONSO. 1948. Anales real soc. españ. fís. y quim. (Madrid). **44B:** 1101–12.

BETTEL, W. 1908. Chem. News. **97:** 158.

BIRINGUCCIO, V. 1540. De la pirotechnia (trans. C. S. Smith & M. T. Gnudi. 1942). Am. Inst. Mining Met. Engrs. : 142.

BOHN, C. 1887. Z. Instrumentenk. **7:** 389–92.

BRANCHI, G. 1818. Répert. pharm. [1] **6:** 77–82.

BRIDGMAN, P. W. 1952. Proc. Am. Acad. Arts Sci. **81:** 165–251.

BRÜHL, J. W. 1879. Ber. deut. chem. Ges. **12:** 204–6.

BUSEY, R. H. & W. F. GIAUQUE. 1953. J. Am. Chem. Soc. **75:** 806–9.

CARLSON, W. A. & L. F. BORCHARDT. 1938. Ind. Eng. Chem. Anal. Ed. **10:** 94–6.

CHINO, Y. 1949. Proc. Japan Acad. **25:** 22-3.

CHRISTIANSEN, C. 1897. Ann. Physik. [3] **62:** 545–68.

CLARK, J. W. 1883. Proc. Phys. Soc. London. **5:** 328–31.

Clarke, F. W. 1878. Am. J. Sci. **16:** 200–1.
Condit, P. C. 1955. Ind. Eng. Chem. **47**(11): 14A.
Cooper, W. C. & N. H. Furman. 1952. J. Am. Chem. Soc. **74:** 6183–6.
Coriou, H., J. Huré & N. Meunier. 1953. Anal. Chim. Acta. **9:** 171–83.
Cowsik, R. K. 1934. Indian J. Phys. **18:** 21–33.
Crafts, J. M. 1887. Bull. soc. chim. [2] **49:** 856–60.
Cueilleron, J. 1944. Bull. soc. chim. France. [5] **11:** 588.
Cueilleron, J., P. Meyer, R. Schneider & J. J. Zeiger. 1949. Bull. soc. chim. France. **1949:** 628–9.
Dauphinee, T. M. 1951. J. Chem. Phys. **19:** 389–90.
Day, H. M. & C. H. Mathewson. 1938. Am. Inst. Mining Met. Engrs. Inst. Metals Div. Technol. Publ. No. 884.
Desha, L. J. 1909. Am. Chem. J. **41:** 152–5.
deWet, J. F. & R. A. W. Haul. 1954. Z. anorg. u. allgem. Chem. **277:** 96–112.
Dittmer, K. H. & R. G. Gustavson. 1940. Ind. Eng. Chem. Anal. Ed. **12:** 297–9.
Dixon, A. E. & J. L. McKee. 1923. J. Chem. Soc. **123:** 895–7.
Dobrowsky, A. 1940. Chem. Ztg. **64:** 32.
Dougherty, M. E. 1943. Chemist Analyst. **32:** 48.
Douglas, T. B., A. F. Ball & D. C. Ginnings. 1951. J. Research. Natl. Bur. Standards. **46:** 334–48.
Dunoyer, L. 1912. Ann. chim. et phys. [8] **26:** 419–32.
Dunstan, W. R. & T. S. Dymond. 1890. Phil. Mag. [5] **29:** 367–72.
Duschak, L. H. & S. O. Spencer. 1917. J. Phys. Chem. **21:** 311–13.
Eberbach Corp. 1956. Bull. 170. Ann Arbor, Mich.
Ewing, C. T., R. E. Seebold, J. A. Grand & R. R. Miller. 1955. J. Phys. Chem. **59:** 524–8.
Forbes, W. R. 1912. Chem. News. **106:** 74.
Foryst, J. 1951. Prace Glównego Inst. Met. **1951:** 307–28.
Gooch, F. A. 1892. Am. J. Sci. [3] **44:** 239–42.
Goux, D. 1953. Chimie & industrie. **70:** 216.
Grossman, M. 1924. Chem. Ztg. **48:** 506.
Haber, F. J. Jaenicke & F. Matthias. 1926. Z. anorg. u. allgem. Chem. **153:** 153–83.
Hackspill, L. & A. Sigot. 1926. Bull. soc. chim. France. [4] **39:** 1281–4.
Hailstone, H. J. 1913. Gas World. **58:** 376–7, 639.
Hallock, W. 1888. Science. **11:** 314.
Hanke, M. E. & M. Johnson. 1933. Science. **78:** 414–5.
Hannay, J. B. 1873. J. Chem. Soc. **26:** 565–74.
Harries, C. & F. Evers. 1921. Z. angew. Chem. **34:** 359, 541–2.
Hayes, J. C. 1955. Anal. Chem. **27**(10): 27A.
Hickman, K. 1929. J. Opt. Soc. Amer. **18:** 62–8.
Hildebrand, J. H. 1909. J. Am. Chem. Soc. **31:** 933–5.
Holmes, F. E. 1946. Ind. Eng. Chem. Anal. Ed. **18:** 451–2.
Hostetter, J. C. & R. B. Sosman. 1918. J. Wash. Acad. Sci. **8:** 11–15.
Hulett, G. A. 1900. Z. physik. Chem. **33:** 611–21.
Hulett, G. A. 1911. Phys. Rev. **33:** 307–16.
Hulett, G. A. & H. D. Minchin. 1905. Phys. Rev. **21:** 388–98.
Hulm, J. K. 1950. Proc. Roy. Soc. London. **A204:** 98–123.
Irvin, N. M. & A. S. Russell. 1932. J. Chem. Soc. **1932:** 891–8.
Isaacs, A. 1932. J. Am. Dental Assoc. **19:** 54–7.
Jaeger, W. 1892. Z. Instrumentenk. **12:** 354–6.
Johnson, W. M. 1901. Elec. World. **37:** 634.
Karsten, B. 1888. Z. Instrumentenk. **8:** 135–7.
Klemm, W. & P. Weiss. 1940. Z. anorg. u. allgem. Chem. **245:** 285–7.
Knipp, C. T. 1906. Science. [N.S.] **23:** 417–8.
Knipp, C. T. 1911. Physik. Z. **12:** 270–1.
Latimer, W. M. 1940. The Oxidation States of the Elements and Their Potentials in Aqueous Solutions. Prentice-Hall. New York, N. Y.
Lewis, D. T. 1953. J. Appl. Chem. London. **3:** 154–60.
Liebhafsky, H. A. 1949. J. Am. Chem. Soc. **71:** 1468–70.
Loomis, N. E. & S. F. Acree. 1911. Am. Chem. J. **46:** 585–97.
Margot, C. 1914. Arch. sci. phys. et nat. **38:** 46–52.
Marshall, A. L., L. F. Epstein & F. J. Norton. 1950. J. Am. Chem. Soc. **72:** 3514–6.
Matthews, H. P. 1936. Soc. Chem. Ind. Victoria Proc. **36:** 1104–6.
Maumené, E. J. 1887. Bull. soc. chim. [2] **49:** 898–9.
Meier von Fürth. 1852. Répert. pharm. [2] **1:** 1–11.

Meyer, L. 1863. Z. anal. Chem. **2:** 241–2.
Meyer, L. 1879. Ber. **12:** 437–9.
Miethe, A. 1924. Naturwissenschaften. **12:** 597–8.
Milazzo, G. 1955. Chimica e industria (Milan). **37:** 195–7.
Millon, M. E. 1846. Ann. chim. et phys. [3] **18:** 333–443.
Moore, B. 1932. Ind. Chemist. **8:** 63–4.
Moore, C. J. 1910. J. Am. Chem. Soc. **32:** 971–2.
Morse, H. N., W. W. Holland & J. L. Carpenter. 1911. Am. Chem. J. **45:** 237–363.
Müller, O. H. 1942. Chem. Eng. News. **20:** 1528.
National Bureau of Standards. 1950–2. Nuclear Data. Circular 499 and Supplements 1, 2, and 3. U.S. Govt. Printing Off. Washington, D. C.
National Research Council. 1926. International Critical Tables. McGraw-Hill. New York, N.Y.
Nayar, P. G. N., V. V. Rao & B. Dasannacharya. 1933. Indian J. Phys. **8:** 91–3.
Nebel, B. 1887. Repert. exp. Physik. **23:** 236–41.
Newbery, E. 1929. Ind. Chemist. **5:** 289–91.
Newbery, E. & S. M. Naude. 1934. Trans. Electrochem. Soc. **64:** 189–200.
Nieman, H. W. & C. W. Nieman. 1952. U.S. 2,583,438.
Palmaer, W. 1899. Ber. **32:** 1391–2.
Pariaud, J. C. & P. Archinard. 1952. Bull. soc. chim. France. **1952:** 454–6.
Patten, H. E. & G. H. Mains. 1917. J. Ind. Eng. Chem. **9:** 600–3.
Penner, S. S. 1948. J. Chem. Phys. **16:** 745–6.
Pfaundler, L. 1879. Repert. exp. Physik. **15:** 328–9.
Pliny the Elder. Natural History. Trans. Bostock and Riley. 1856. Bell and Sons. London, England.
Post, B. & C. F. Hiskey. 1950. J. Am. Chem. Soc. **72:** 4204–8.
Prausnitz, P. H. 1921. Z. angew. Chem. **34:** 443.
Proctor, W. G. & F. C. Yu. 1949. Phys. Rev. **76:** 1728–9.
Pugachevich, P. P. 1947. J. Exptl. Theoret. Phys. (U.S.S.R.) **17:** 648–54.
Richards, T. W. & J. H. Wilson. 1909. Carnegie Inst. Pub. No. 118. Washington, D. C. (also, 1910. Z. physik. Chem. **72:** 129–201).
Riesenfeld, E. H. & W. Haase. 1925. Ber. deut. chem. Ges. **58:** 2828–34.
Riesenfeld, E. H. & W. Haase. 1926. Ber. deut. chem. Ges. **59:** 1625–9.
Robeson, F. L. 1929. J. Opt. Soc. Amer. **18:** 72–4.
Rotariu, G. J., E. Schramke, T. S. Gilman & J. H. Hildebrand. 1951. J. Am. Chem. Soc. **73:** 2527–8.
Russell, A. S. 1929. J. Chem. Soc. **1929:** 2398–401.
Russell, A. S. & D. C. Evans. 1925. J. Chem. Soc. **127:** 2221–30.
Seddig, M. & G. Haase. 1949. Kolloid-Z. **114:** 169–74.
Sivaramakrishnan, M. V. 1929. Indian J. Phys. **13:** 205–7.
Smith, E. F. & L. K. Frankel. 1889. J. Franklin Inst. **127:** 469-73
Smith, F. J. 1890. Phil. Mag. [5] **29:** 501–3.
Spedding, F. H. & J. L. Dye. 1955. J. Phys. Chem. **59:** 581–3.
Spicer, W. M. & C. J. Banick. 1953. J. Am. Chem. Soc. **75:** 2268–9.
Spicer, W. M. & H. W. Bartholomay. 1951. J. Am. Chem. Soc. **73:** 868–9.
Steinwehr, H. v. & A. Schulze. 1929. Z. Instrumentenk. **49:** 566–7.
Stock, A., F. Cucuel, F. Gerstner, H. Köhle & H. Lux. 1934. Z. anorg. u. allgem. Chem. **217:** 241–53.
Stromberg, A. G. 1952. Doklady Akad. Nauk S.S.S.R. **85:** 831–4.
Strong, J. D. 1938. Procedures in Experimental Physics. Prentice Hall. New York, N. Y.
Sunier, A. A. & C. B. Hess. 1928. J. Am. Chem. Soc. **50:** 662–8.
Sunier, A. A. & C. M. White. 1930. J. Am. Chem. Soc. **52:** 1842–50.
Tammann, G. & J. Hinnüber. 1927. Z. anorg. u. allgem. Chem. **160:** 249–70.
Tiede, E., A. Schleede & F. Goldschmidt. 1926. Ber. **59:** 1629–41.
Vogels, H. 1934. Bull. soc. chim. Belg. **43:** 327–30.
Wailes, R. B. 1930. Chemist Analyst. **19**(1): 16.
Waran, H. P. 1926. Phil. Mag. [7] **2:** 317–20.
Weber, L. 1879. Repert. exp. Physik. **15:** 50–3.
Weinhold, A. 1873. Repert. exp. Physik. **9:** 69–83.
Wetzel, J. 1909. Z. anal. Chem. **48:** 470–2.
Wichers, E. 1942. Chem. Eng. News. **20:** 1111–2.
Wild, H. 1871. Repert. exp. Physik. **7:** 256–9.
Wolff, F. A. & C. E. Waters. 1907. Bull. Bur. Standards. **3:** 623–40.
Wright, A. W. 1881. Am. J. Sci. [3] **22:** 479–84.

THE GROWTH OF MERCURY CRYSTALS FROM THE VAPOR

By Gerald W. Sears
Research Laboratory of the General Electric Company, Schenectady, N. Y.

Introduction

Studies of the growth mechanism of mercury in both the crystalline and liquid phases have contributed to the development of current concepts of the molecular processes involved in the growth of crystals. It is the purpose of the present paper to describe the growth behavior of mercury "whiskers" and platelets from the vapor phase and to account for their growth behavior. It will be shown that the growth kinetics for both whiskers and platelets lead to the conclusion that these crystals are nearly perfect.

Since the present status of the theory of the growth of crystals may not be completely familiar to the reader, the description and discussion of the present studies will be preceded by a short summary of the accepted mechanisms of the growth and evolution of crystals.

Mechanisms of Crystal Growth

The first critical consideration given to the molecular kinetics involved in the crystal growth process is ascribed to Willard Gibbs.[1] It had been pointed out that the growth of a *perfect crystal* surface must proceed by nucleation of a monolayer island on a perfect crystal face and by the lateral growth of the monolayer nucleus to the extremities of the surface. Gibbs made the deduction, on a kinetic basis, that the formation of a 2-dimensional nucleus would not proceed at vapor pressures infinitesimally greater than the equilibrium value. The nucleation would occur at an appreciable rate at supersaturations in excess of a critical value.

The free energy of formation of a monolayer "pillbox" consists of a surface term and a volume term. For a supersaturated vapor phase, the volume contribution is negative. The surface term is positive under all circumstances. Since the volume term is proportional to the square of the pillbox radius, while the surface term is linearly proportional to the radius, it follows that the surface contribution to the free energy will predominate at small radii, while the volume contribution will predominate at large radii. The general course of the free-energy curve as a function of pillbox radius for a fixed supersaturation in the vapor phase is shown in FIGURE 1. The maximum in the free-energy curve represents a free-energy barrier that each embryonic pillbox must surmount to become a stable nucleus.

The kinetics of 2-dimensional nucleation have been treated quantitatively by Kossel,[2] Stranski,[3] Becker and Doring,[4] and Frenkel.[5] It is concluded that there is a critical supersaturation below which a perfect crystal face should not grow, and above which the rate of growth should be determined by the material transport rate to the advancing surface.

The rate equation for 2-dimensional nucleation is derived briefly. If a pillbox has a radius, r, and is a monolayer in thickness, the free energy of forma-

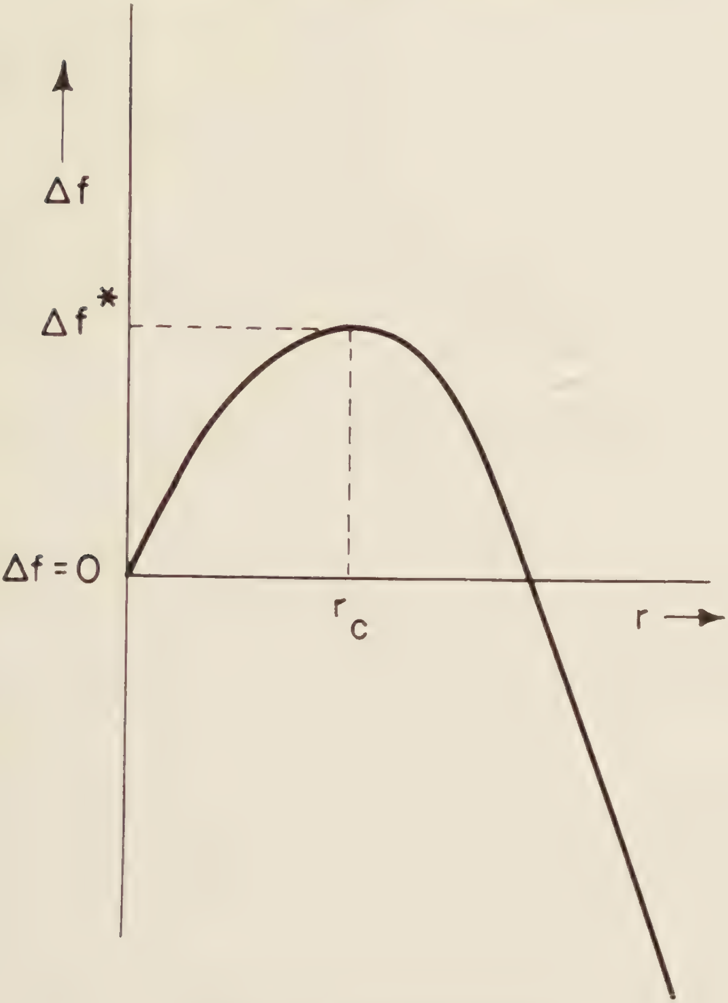


FIGURE 1. Free energy versus radius.

tion, Δf, is given by

$$\Delta f = 2\pi r a \gamma + \pi r^2 a \, \Delta F_V \tag{1}$$

where γ is the specific surface free energy of the peripheral surface, a is the interplanar distance, and ΔF_V is the volume-free energy for vapor deposition. Since the free energy versus radius curve shown in FIGURE 1 has a maximum, EQUATION 1 is differentiated with respect to the radius and equated to zero.

$$\left(\frac{2\Delta f}{2r}\right)_{r=r_c} = \frac{\delta \Delta f}{\delta r_{r=r_c}} = 2\pi a \gamma + 2\pi r_c a \Delta F_V = 0 \tag{2}$$

The value of the radius, r_c , at the maximum may be obtained from EQUATION

2 to give

$$r_c = -\frac{\gamma}{\Delta F_V} \tag{3}$$

The height of the free-energy maximum, Δf^*, may be written

$$\Delta f^* = \Delta f(r_c) = -\frac{\pi a \gamma^2}{\Delta F_V} \tag{4}$$

According to the rate theory developed by Becker and Doring[1] and Volmer and Schultze,[6] the number, $\dot{N}$, of 2-dimensional nuclei formed per second on 1 cm.[2] of surface is given by

$$\dot{N} = Be^{-\Delta f^*/kT} \tag{5}$$

where $B \sim 10^{20}$ sec.$^{-1}$, k is the molecular gas constant and T is the absolute temperature. Combining EQUATIONS 4 and 5, it is found that

$$\dot{N} = Be^{\pi a \gamma^2/kT\Delta F_V} \tag{6}$$

The volume-free energy can be written in terms of the supersaturation ratio

$$\alpha = P/P_o \tag{7}$$

where P is the actual pressure of depositing vapor and P_o is the vapor pressure to give

$$\Delta F_V = -\frac{\rho RT}{M} \ln\alpha \tag{8}$$

where ρ is the density of the condensed phase, R is the molar gas constant, and M is the molecular weight.

The combination of EQUATIONS 6 and 8 yields the usual form of the rate equation for 2-dimensional nucleation.

$$\dot{N} = Be^{-\pi a \gamma^2 M/\rho kRT^2 \ln\alpha} \tag{9}$$

The growth rate of a perfect crystal face as a function of supersaturation is depicted in FIGURE 2. Underlying the concept of growth by 2-dimensional nucleation is the basic assumption that the advancing surface is atomically smooth. An atomically smooth surface is one that has no positions at which a molecule can attach to the crystal and be bound by the full heat of sublimation. On the basis of crystal models all low-index planes, for example, {100}, {110} should be atomically smooth.

The first empirical study of crystal growth rate as a function of supersaturation was reported by Volmer and Schultze[6] in 1931. These investigators established the fact that there existed no critical supersaturation below which growth for phosphorus and naphthalene ceased. For iodine it was observed that the rate of growth approximated the square of the supersaturation at very low supersaturations. None of the growth-rate curves was in agreement

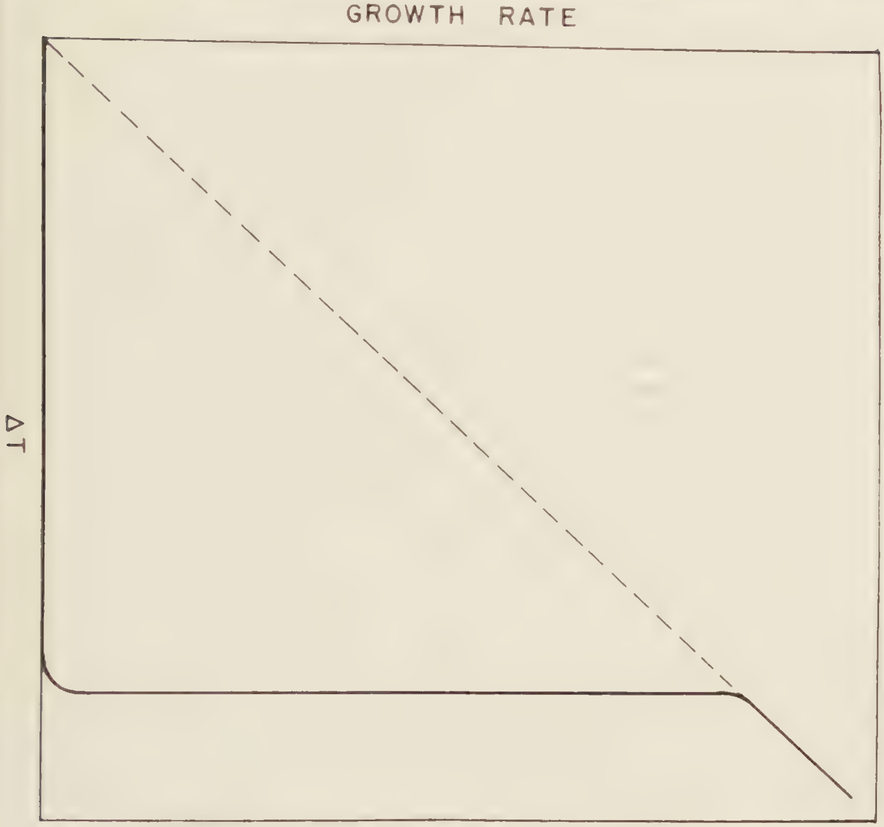


FIGURE 2. Theoretical growth rate of a perfect crystal.

with the predicted growth behavior for a 2-dimensional nucleation process. The suggestion was made that the crystal surfaces were covered by a self-adsorbed mobile layer in equilibrium with the crystal surface. This supposition is equivalent to the assumption of a rough surface.

The concept needed to rationalize the growth-rate data of Volmer and Schultze[6] was advanced in 1949 by Frank,[7] who pointed out that growth behavior, as well as the mechanical properties of real crystals, could be accounted for by the assumption of line defects called dislocations. Frank emphasized that the critical sites on a growing crystal surface were the growth steps. At such a step, transfer from the self-adsorbed layer to the crystalline phase occurred. Two-dimensional nucleation provided transient growth steps that grew themselves out of existence. Frank pointed out that the intersection of a screw dislocation with the crystal surface (FIGURE 3) presented a permanent growth step that revolved about the screw axis and generated a spiral pattern as growth occurred.

The observation of spiral growth traces[8] on a wide variety of crystals offered immediate confirmation of the Frank mechanism. In the growth of CdI_2

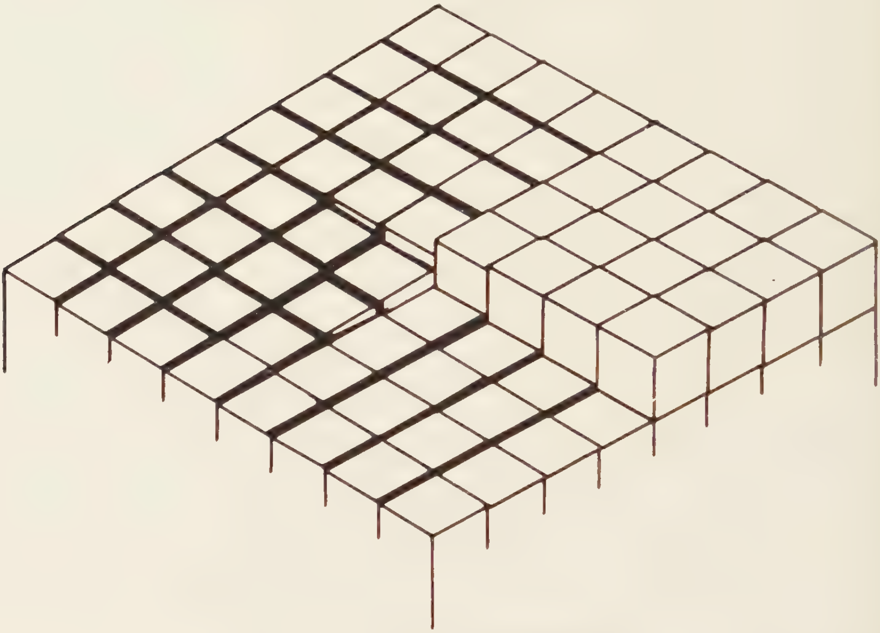


FIGURE 3. Emergent screw dislocation.

platelets from aqueous solution,[9, 10] motion pictures showing the screw dislocation in operation are available.

The growth of crystals by the screw-dislocation mechanism has been subjected to detailed analysis by Burton, Cabrera, and Frank.[11] Burton and Cabrera[12] have demonstrated that low-index faces are indeed smooth by detailed theoretical analysis. The concept of the surface smoothness of low-index surfaces at present, however, can be confirmed by a simple argument. No surface that bears a spiral growth trace could be rough. If such a surface were rough, growth sites would be distributed everywhere on the surface. The screw-dislocation step would not be a favored competitor for impinging atoms, and the step would not rotate during growth. Since it does rotate, this step is a favored growth site, and the surface is atomically smooth.

GROWTH OF MERCURY CRYSTALS

In 1921, Volmer and Estermann[13] reported the formation of tiny platelets of mercury by the condensation of mercury vapor upon a blown-glass surface at −63.5° C. The platelets of mercury grew to a length of about 0.3 mm. and were so thin that they underwent ceaseless Brownian motion. The pressure of mercury vapor in the closed evacuated chamber was controlled by regulating the temperature of mercury in a reservoir. Platelets were observed to grow in about 2 min. when the temperature of the reservoir was maintained at −10° C. This pressure of mercury vapor was 1600 times the vapor pressure at −63.5° C.

The rate of growth of platelets in their large dimension was a thousandfold greater than could be accounted for by the direct impingement and condensation of mercury atoms upon the advancing plane from the vapor phase. Volmer and Estermann[13] concluded that the impinging mercury atoms were adsorbed on the solid surface and that the adsorbed atoms migrated over the surface until they either evaporated or were incorporated into the solid lattice.

Langmuir[14, 17] has concluded from studies of the interaction of gases with solid surfaces that gas molecules striking a solid surface are temporarily adsorbed before they are re-evaporated. The process of impingement, temporary adsorption, and re-evaporation is the general mechanism for reflection of gas molecules at a solid surface.

It seemed desirable to repeat the experiments of Volmer and Estermann[13] in the light of Frank's proposals concerning the mechanism of crystal growth. To clarify the presentation, the growth mechanisms of mercury whiskers and platelets will be discussed separately, although the experimental details will be described in the same section. The results have been described previously by the author.[18, 19, 20]

Experimental Methods

The initial experiments were carried out using a vessel illustrated in FIGURE 4. The liquid mercury that supplied the vapor for crystal growth was contained in the reservoir, *R*. The crystals were grown on the condensation finger, *F*. The reservoir was filled with a few milliliters of liquid mercury and then sealed onto a vacuum system by means of a seal-off constriction. The vacuum line consisted of a 2-stage diffusion pump backed by a mechanical pump. Since there was mercury vapor throughout the system, no liquid-air trap was used. The pressure was measured with a McLeod gauge.

The vessel was evacuated 24 hours before being sealed. The vessel and the mercury were heated with a torch for about 1 hr. in the early stages of evacuation. The McLeod gauge indicated a permanent gas pressure of about 10^{-6} mm. at the time of sealing. This pressure insured that molecular flow was operative between the mercury reservoir and the finger. After the vessel was sealed, it was ready for use in an indefinite number of experiments.

In later experiments the vessel shown in FIGURE 5 was used. This vessel had an additional feature: not only was the pressure of mercury vapor over the finger controlled, but the vapor temperature was controlled also. In addition to the reservoir, *R*, and the finger, *F*, there was a built-in Dewar vessel, *A*, to control the temperature of condensing mercury vapor. The reservoir was filled with mercury. The crystal grower was evacuated, baked, and sealed off according to the same schedule employed for the vessel of FIGURE 4. In crystal-growth experiments in the final vessel, 3 temperatures were controlled. The condensation temperature, T_c, was established at −63.5° C. by a bath of partially frozen chloroform in the condensation finger. The temperature of the mercury vapor, T_v, was controlled by an acetone bath in the built-in Dewar vessel, *A*. The reservoir temperature, T_r, was controlled by immersion in an acetone bath contained in a separate Dewar flask. The temperature of the acetone baths was controlled manually. Dry-ice fragments were added to lower the temperature; copper strips were introduced to raise the tempera-

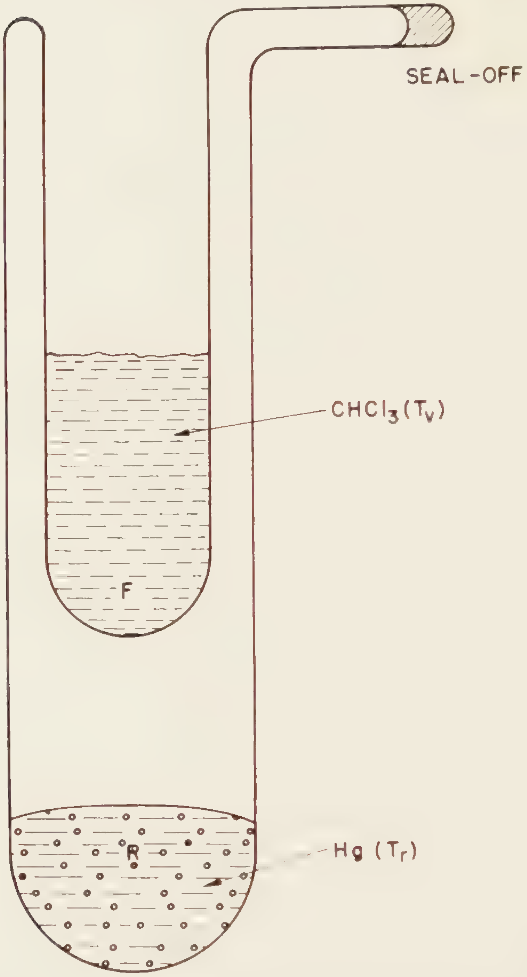


FIGURE 4. The first growth vessel used in these experiments.

ture. The mercury crystals were observed with a 5× magnifier through a port, *P*. To measure whisker lengths, a low-power telescope that superimposed a scale on the image was used.

For crystal growth, temperatures T_v, T_r, and T_c were adjusted, in that order. The reservoir temperature, T_r, was then slowly allowed to rise until crystal formation was observed. T_c was always held at −63.5° C.

RESULTS

Growth Conditions

When the vapor temperature, T_v, was 25° C., all crystals were thin platelets, in agreement with the results obtained by Volmer and Estermann.[13] On

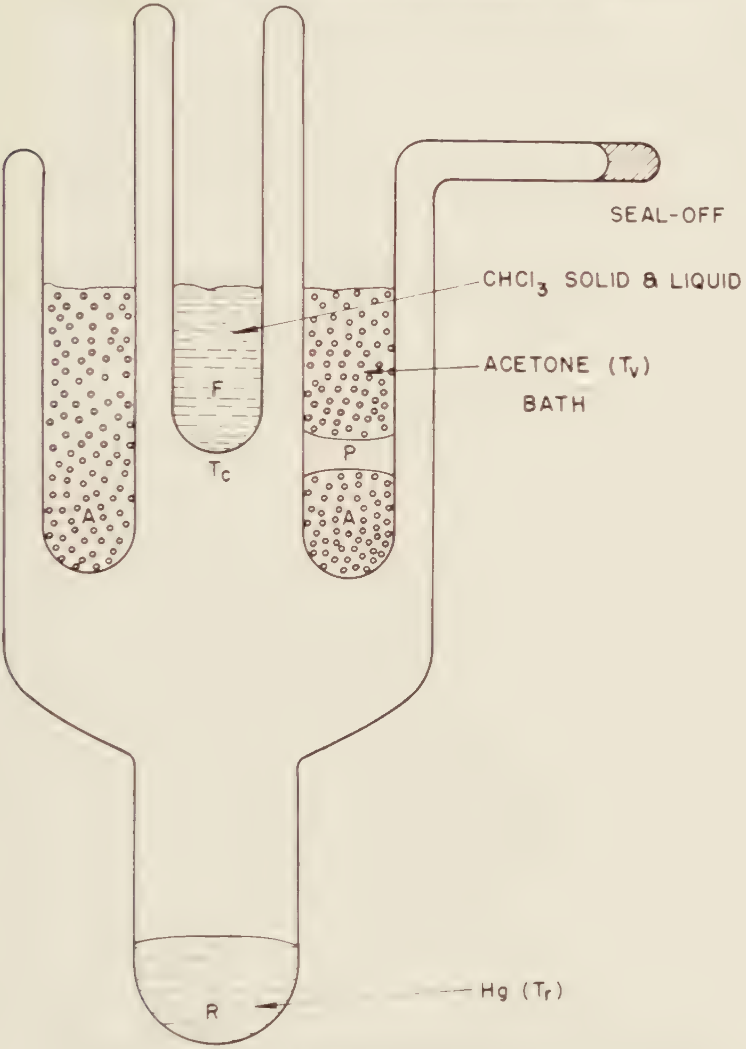


FIGURE 5. The second growth vessel used in these experiments.

a freshly blown Pyrex surface, platelets formed very sparsely on the condenser finger when the reservoir temperature, T_r, reached $-14°$ C. from a colder temperature. A plentiful population of platelets was estimated to increase a thousandfold with an increase in T_r from $-13°$ C. to $0°$ C. This increase in temperature corresponds to a doubling of the supersaturation ratio.

If a blown Pyrex finger was carelessly handled before use and, presumably, scratched or chipped, a few platelets formed at $T_r = -25°$ C. An optically polished Pyrex surface yielded a patchlike gray film of mercury at $T_r = -35°$ C. No platelets were observed.

TABLE 1

Substrate	T_r(°C.)	T_v(°C.)	T_c(°C.)	Growth habit
Blown Pyrex	−14	25	−63.5	Platelets
Polished Pyrex	−35	25	−63.5	Patchlike film
Vitreous quartz	−25	25	−63.5	Whiskers, few plates
Blown Pyrex	−40	25	−78	Whiskers
Blown Pyrex	−30	−50	−63.5	Whiskers

For $T_v = -50°$ C., $T_r = -30°$ C., only whiskers of crystalline mercury were grown. It was observed that for $T_v > -50°$ C., mixed platelets and whiskers formed. For $T_v \sim -20°$ C. and above, only platelets grew. It was also observed for $T_v = -50°$ C. in a given experiment that as T_r increased from −30° C., the whisker population increased, and at the highest supersaturations, $T_r \sim -15°$ C., platelets appeared.

A growth vessel was constructed with a vitreous quartz condenser finger. With $T_v = 25°$ C., $T_r = -25°$ C., and $T_c = -63.5°$ C., whiskers were predominant and a very few platelets grew. The whiskers were quite short, and they rapidly thickened to give interference colors under illumination by white light.

It was observed for $T_c = -78°$ C., $T_v = 25°$ C., and $T_r = -40°$ C. that mercury whiskers could be grown on a blown Pyrex substrate.

These conditions of growth are summarized in TABLE 1.

Supersaturation Ratios

For $T_v = -50°$ C., the first whiskers appeared at a supersaturation ratio of about 100. If $T_v = 25°$ C., the first platelets appeared at a supersaturation ratio of about 1600. This latter observation agreed well with that of Volmer and Estermann.[13] When the supersaturation ratio was increased over the appearance value, the crystal population increased.

Appearance Kinetics

When the reservoir temperature, T_r, was such as to furnish a mercury vapor pressure less than a critical pressure to nucleate and grow crystals, no crystals would appear in a very long time. If T_r was allowed to rise until the critical supersaturation was reached, crystals began to appear within a few minutes. If T_r was held constant, the number of crystals per unit area of finger surface stayed perceptibly fixed over a long period. A further temperature increase gave rise to an increase in crystal population in 10 to 20 min. A new fixed temperature was accompanied by a cessation in the appearance of new crystals. The free-energy change driving nucleation and growth is controlled by the supersaturation of mercury vapor over the cold finger.

The appearance kinetics for both platelets and whiskers were alike, although they appeared under differing T_v and T_r. The concentration of crystals was dependent on T_r and not on time for a fixed T_v. The population of crystals on the condensation finger was static for a given mercury pressure, and was independent of the time allowed for growth. It was estimated roughly for $T_c = -63.5°$ C. and $T_r = 25°$ C., that the crystal population was one thousandfold larger for a vapor pressure of 4.2×10^{-5} mm. than for 1.9×10^{-5} mm. Hg.

Kinetics of Whisker Growth

In a typical experiment the whiskers were first observed as tiny dots on the condenser finger. As the whiskers grew longer they began to bend in Brownian motion. Each whisker reached a certain length in about 30 min. that is designated as its terminal length. The terminal lengths, for the most part, ranged from 0.25 to 1.25 mm., with very few whiskers attaining lengths of 2.5 mm. The longest whiskers made their appearance at the highest supersaturations. The whisker remained at a constant radius throughout the axial growth to terminal length. At the attainment of terminal length, the axial growth rate abruptly diminished to an immeasurable rate. Just as abruptly, the radial growth started. The radial growth was indicated by a cessation of Brownian motion, and it was followed by the cyclic appearance of interference colors, blue through red. The rate of change of interference colors offers a precise technique for measuring radial growth rate. It has been impossible to make more than a rough measurement of axial growth rate.

A selected crystal is visible under an arbitrary illumination if viewed through a small solid angle. If the observation and illumination directions are fixed, a given whisker appears and disappears occasionally.

The whiskers in Brownian motion were observed to deflect at the thin ends by about 0.1 mm. in 1.0 mm. length. The platelets moved so that the motion normal to the platelet remained in a single plane. It was observed that certain prominent whiskers appeared at the same location in successive experiments on a given condensation surface. These whiskers were either unusually long or unusually bright.

Kinetics of Platelet Growth

For $T_r = -12°$ C. the platelets grew to their ultimate lateral extent of 0.3 mm. in approximately 2 min. The platelets underwent Brownian motion at this stage and, over a period of approximately half an hour, they ceased their agitation. When a platelet was illuminated with a parallel beam of light, a bright spot was projected onto the walls of the vessel. The magnitude of the Brownian motion was estimated by observing the motion of the spot. At a distance of 50 mm. from a platelet a motion of approximately 2 mm. was observed. This corresponds to approximately a 2° angular deflection.

Platelet Crystal Habit

The platelets were attached to the substrate by a corner. The most common shape is shown in FIGURE 6, where adjacent angles were approximately 108° and 72°. It is probable that the platelet is bounded on all faces by rhombohedral {100} planes. The maximum lateral dimensions were 0.3×0.3 mm.^{2}, and the platelet thickness was estimated by Volmer and Estermann[13] to be 0.03μ.

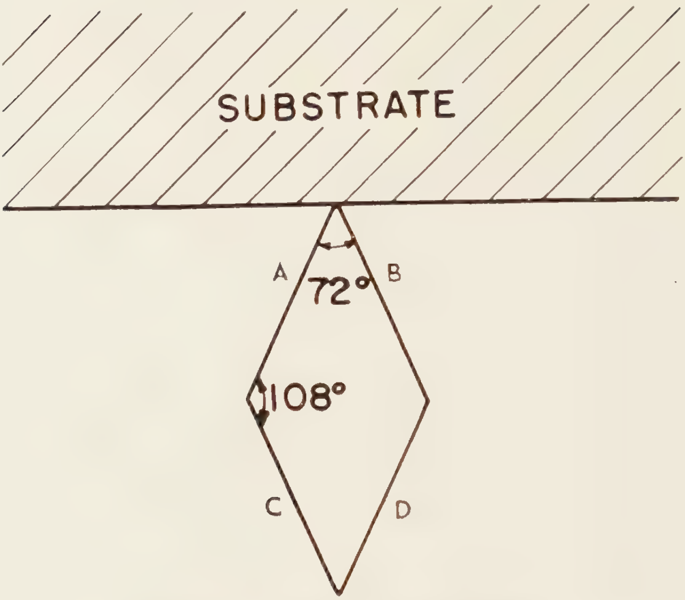


FIGURE 6. Diagram of a mercury platelet.

Melting of Platelets

The temperatures T_c and T_v were allowed to rise simultaneously to the melting point of mercury. There was a melting range of approximately 5° C. Only the disappearance of the platelet was observed, not the resulting liquid phase. The platelets in Brownian motion disappeared about 5° C. under the melting point. It was assumed that fusion was involved, rather than evaporation and condensation on a neighboring particle of greater thickness.

DISCUSSION

Whisker Growth

It is known from electron-microscopic evidence[15] that a glass surface is, for the most part, smooth like a liquid surface, but that tiny crystalline regions are scattered here and there in the vitreous whole. It is proposed that solid mercury nucleates on the crystalline regions that present exposed screw-dislocation ends. The screw dislocation in the crystallite is transposed to a screw dislocation in mercury, and the mercury crystal grows outward from the glass in the form of a whisker. The whisker will be bounded parallel to its axis by low-index or close-packed planes, since these have the lowest surface energy and will give the whisker the minimum free energy.

This discussion will present the syntheses of the preceding mechanism from experimental evidence and the consequences of this mechanism. The arguments proceed from calculations of whisker radius and growth rate. These are calculations presented below.

Whisker radius. The bending that a whisker undergoes in Brownian motion can be used to estimate the radius of the whisker. If the average deflection of the end of a whisker is $\bar{\delta}$, its average kinetic energy E is given by

$$\bar{E} \approx 1/2\, K\bar{\delta}^2 \tag{10}$$

where K is the Hooke's law constant for deflection of the whisker and $\bar{\delta}^2$ is approximated for $\bar{\delta^2}$. The principle of equipartition of energy states that the average thermal energy per particle per degree of freedom for a harmonic oscillator is kT, where k is the molecular gas constant. We write

$$\bar{E} = kT \tag{11}$$

since only 1 degree of freedom is observed. T is the absolute temperature of the whiskers.

The Hooke's law constant, K, can be evaluated from the theory of elasticity. A circular cross section is assumed, although it will be shown in a later section that the whisker has a polygonal cross section. If r is the whisker radius, l is the whisker length, and E is Young's modulus for solid mercury, it can be written that

$$K = \frac{3\pi r^4 E}{4l^3} \tag{12}$$

If EQUATIONS 10, 11, and 12 are combined, it may be written that

$$kT = 1/2\, \frac{3\pi}{4}\, \frac{r^4 E}{l^3}\, \bar{\delta}^2 \tag{13}$$

EQUATION 13 is solved for r:

$$r = \left\{\frac{8l^3 kT}{3\pi E\bar{\delta}^2}\right\}^{1/4} \tag{14}$$

It will be recalled that $l = 1$ mm. and $\bar{\delta} = 0.1$ mm. Young's modulus is 10^{11} dynes/cm.^{2} for mercury. The radius of the whisker is found to be about 0.01μ.

Rate of growth. When a whisker is formed at a reservoir temperature of $-30°$ C., the time lapse until the appearance of a full-sized whisker is about 20 min. The time between the first sign of a whisker and its attainment of a length of 1 mm. is about 10 min. The average rate of growth is, therefore, about 1.5×10^{-4} cm./sec. The mass rate of impingement, $\dot{W}$, of mercury atoms on the end of the whisker is given by

$$\dot{W} = \pi r^2 p \sqrt{\frac{m}{2\pi kT}} \tag{15}$$

where r is the radius of the whisker, p is the pressure of mercury over the whisker, m is the mass of a mercury atom, k is the molecular gas constant, and T is the absolute temperature of the vapor phase. If it is assumed that every atom that strikes the end of the whisker is incorporated into the mercury lattice, and if the radius of the whisker is constant, it can be written that

$$\pi r^2 \rho \dot{l} = \dot{W} \tag{16}$$

where $\dot{l}$ is the rate of length increase and ρ is the density of solid mercury. By combining EQUATIONS 15 and 16 and solving for $\dot{l}$, it is found that

$$\dot{l} = \frac{p}{\rho} \sqrt{\frac{m}{2\pi kT}} \tag{17}$$

The vapor pressure of mercury at −30° C. is about 7×10^{-6} mm. Hg. The rate of growth calculated from EQUATION 4 is given by

$$\dot{l}_{\text{calc.}} = 3 \times 10^{-8} \text{ cm./sec.} \tag{18}$$

The actual rate of growth is 5000 times the calculated rate of growth. If the assumption of a constant whisker radius had not been made, the calculated rate of growth would have been even smaller, and the discrepancy between calculated and measured rates of growth would have been larger.

The calculated rate of growth is based on the hypothesis that only mercury atoms striking the advancing end of the whisker contribute to axial growth. The discrepancy between the measured and the calculated rates of growth demonstrates that mercury atoms striking elsewhere on the mercury and/or glass surface are contributing to axial growth.

Surface nucleation. Consider now the nucleation of a new layer of mercury on the surface of a low-index plane. The nucleation rate, $\dot{N}$, in nuclei/cm.^{2}/sec. for surface nucleation is given by EQUATION 9.

The surface nucleation rate necessary to account for an axial rate of growth of 1.5×10^{-4} cm./sec. can be calculated if it is assumed that each new layer grows to full size instantaneously.

A layer of mercury is about 3×10^{-8} cm. thick. It is necessary to nucleate 5000 layers per second. Since the whiskers are 0.01μ in radius, their end area is 3×10^{-12} cm.^{2}, and the rate of nucleation needed to allow a rate of growth of 1.5×10^{-4} cm./sec. is

$$\dot{N} \cong 2 \times 10^{15} \text{ nuclei/cm.}^2\text{/sec.} \tag{19}$$

The logarithmic form of EQUATION 9 is solved for $ln\alpha$ as follows:

$$ln\alpha = \frac{\pi a \sigma^2 M}{\rho RT ln \frac{B}{\dot{N}}} \tag{20}$$

EQUATION 20 is solved for σ with the constants $B = 10^{20}$ sec.$^{-1}$, $\sigma = 500$ ergs/cm.^{2} The value of supersaturation necessary to cause a growth rate of 1.5×10^{-4} cm./sec. is

$$\alpha = p/p_o = 10^{24} \tag{21}$$

It might be argued that, for such a large rate of nucleation, significant error might be involved in the use of EQUATION 20. The magnitude of the discrepancy between the calculated supersaturation ratio of 10^{24} and the measured ratio of 10^2 to 10^3 for the growth rate in question, however, leaves no doubt that the axial growth mechanism does not involve the nucleation of new layers. Even to nucleate a single surface nucleus cm.^{2} sec. would require a supersaturation ratio of 4×10^6.

Axial growth mechanism. Since it has been established that the axial growth rate cannot be accounted for by homogeneous 2-dimensional nucleation, it must be postulated that a permanent growth step is exposed in the advancing face. This is equivalent to the statement that the whisker contains an axial screw dislocation.

The phenomenal rate of growth still must be rationalized. It has already been postulated on thermodynamic grounds that a whisker is bounded by low-index faces parallel to its axis. Since 2-dimensional nucleation cannot occur on these faces, a mechanism is provided for rapid axial growth. Mercury atoms impinge on the sides of the whisker, are adsorbed, and migrate to the advancing end, where they are incorporated into the crystal lattice. If it is assumed that all atoms within a distance, λ_x, of the end contribute to the axial growth, then it can be written that

$$2\pi r\lambda_x + \pi r^2 = 5000\pi r^2 \tag{22}$$

Ignoring the second term of the left side of EQUATION 16 and solving for λ_x

$$\lambda_x = 2500r \tag{23}$$

It has been calculated that $r = 0.01\mu$, so that $\lambda_x = 0.025$ mm. The quantitative expression for the axial growth rate is then given by

$$\dot{l} = \frac{2\lambda_x}{r}\frac{p}{\rho}\sqrt{\frac{m}{2\pi kT}} \tag{24}$$

Burton, Cabrera, and Frank[11] have shown theoretically that an atom adsorbed on a solid surface has a finite lifetime, τ_s, before evaporation. It is presumed that the adatom in the meanwhile does not encounter a site of growth where it is incorporated into the solid lattice. The average distance an adatom moves between adsorption and evaporation is called the mean displacement of adsorbed molecules. This distance is just λ_x, which was introduced in EQUATION 22.

In any condensation process the net condensation rate is the difference between the impingement rate and the evaporation rate. In the preceding calculations it has been assumed that the evaporation rate can be neglected. This approximation is justifiable for the high supersaturation ratios used, from 70 upwards, since the supersaturation ratio is equal to the ratio of the rate of impingement to the rate of evaporation.

Since a mercury whisker must have a higher rate of evaporation than bulk mercury at the same temperature, it must be proved that the vapor pressure, p_w, of a whisker does not exceed the vapor pressure of bulk mercury by a large factor. If p_o is the vapor pressure of bulk mercury at temperature, T,

$$ln \frac{p_w}{p_o} = \frac{2\gamma M}{\rho r R T} \tag{25}$$

where γ is the surface free energy of solid mercury, M is the atomic weight, ρ is the density, r is the fiber radius, and R is the gas constant. Assuming $\gamma = 500$ ergs/cm.^{2} as a reasonable value, it is calculated that $p_w/p_o = 2$ for $r = 0.01\mu$.

The minimum ratio of p/p_o is 50, where p is the pressure of mercury in the vapor phase, and the neglect of evaporation is justified. The increase of vapor pressure associated with the presence of an axial screw dislocation is only 1 per cent of the bulk vapor pressure, so this contribution is entirely negligible.

Nucleation. The final mercury whisker appears to be a perfect crystal except for an axial screw dislocation. The result could have arisen by 2 possible mechanisms: either the original nucleus contained a screw dislocation, or the original nucleus was a perfect crystal and a screw dislocation was introduced later. The available evidence supports the former mechanism.

It has been shown already that mercury cannot nucleate on the surface of mercury at an appreciable rate for the experimental supersaturations used. It follows that it would be even more difficult to nucleate on a perfect foreign crystal, and most difficult on a vitreous surface. Beyersdorf[21] has published electron micrographs of fractured glass showing crystallites ranging from 0.002 to 0.02μ in diameter. The crystallites with emergent screw dislocations would offer sites where solid mercury could nucleate. The mercury nuclei would have the built-in screw dislocations necessary for rapid growth. The crystallites without screw dislocations would be ineffective.

Mercury nuclei might also form at the steps bounding terraces; however, no repeatable step would form, and growth would cease under the supersaturation used experimentally.

It should be pointed out that the postulated mechanism predicts the repetitive formation of whiskers at a given site under like conditions. It has been observed experimentally that certain distinctive whiskers form repeatedly at a given site on the finger. These whiskers are distinguished by their length, direction of growth, or brightness.

Radial growth. It is now necessary to rationalize the cessation of rapid axial growth at constant radius, and the initiation of a normal radial growth rate when a terminal length is reached. Since homogeneous surface nucleation is excluded, it must be assumed that new layers can be nucleated at the substrate-mercury corner at the base of each whisker.

Since the end of a whisker is a sink for adsorbed mercury atoms, the surface concentration of adatoms will vary over the surface and will be a minimum at the whisker end. Conversely, if a whisker was evaporating, the surface concentration would be a maximum at the emergent screw dislocation.

If τ_s is the mean lifetime of an adsorbed mercury atom, and σ^* is the surface concentration in equilibrium with mercury vapor of pressure, p

$$\sigma^* = \frac{p\tau_s}{\sqrt{2\pi mkT}} \tag{26}$$

It can be shown that, if $\sigma(x)$ is the steady-state surface concentration at coordinate x on a fiber, where $x = 0$ is taken at the free whisker end,

$$\sigma^* - \sigma = (\sigma^* - \sigma_o)e^{-x/\lambda_x} \tag{27}$$

Here σ_o is the adatom concentration in equilibrium with the whisker. At the whisker end $x = 0$ and $\sigma = \sigma_o$. Away from the end, EQUATION 27 may be simplified, since $\sigma^* \gg \sigma_o$.

$$\sigma = \sigma^*(1 - e^{-x/\lambda_x}) \tag{28}$$

As a whisker grows long,

$$\sigma \longrightarrow \sigma^* \tag{29}$$

at its base. The original mercury crystal grew radially to the whisker radius at a critical pressure p, but not at a pressure below p. Hence the whisker should again begin to grow radially by the intermediation of the substrate whisker corner when the surface concentration approaches σ^* if the whisker radius is less than the radius of the crystallite upon which it grew. Such whiskers should grow only a few multiples of λ_x long. Experimentally, many whiskers are observed fulfilling this length requirement. The other extreme is the situation where the whisker and crystallite radii are nearly equal. Radial growth over the glass requires a higher surface concentration than σ^*. Such whiskers are probably represented by those that are observed with lengths up to 1 to 2 mm. When the mercury pressure in the system is raised by increasing the temperature of the reservoir, these whiskers may also thicken radially. Intermediate cases would involve radial growth partly over crystallite and partly over glass. These would grow to intermediate length.

Surface diffusion. In a previous section a value of 0.025 mm. has been calculated for the mean free path of a mercury atom adsorbed on a mercury surface. This value is estimated for the planes parallel to the axis of the whisker. It is reasonable that these planes are rhombohedral $\{100\}$ planes. The $\{100\}$ planes present the closest packing, a 3.00 Å. interatomic spacing, and should have the lowest surface free energy. This habit should give the thermodynamically most stable crystal. An adsorbed atom on the rhombohedral $\{100\}$ plane would be expected to be bonded to 4 atoms in the adsorbent plane, but at 3.47 Å. separation instead of 3.00 Å., since the interatomic distance of atoms in adjacent $\{100\}$ planes is the former.

Burton, Cabrera, and Frank[11] have derived equations by which the mean surface displacement can be estimated. They demonstrated that

$$\lambda_x = a \cdot e^{\{W'_s - U_s/2kT\}} \tag{30}$$

where U_s is the activation energy for transfer of an adsorbed molecule between neighboring adsorption sites, W'_s is the energy of evaporation from the adsorbed layer to the vapor, a is the interatomic spacing, and k is the molecular gas constant. McKenzie[22] has calculated that U_s is only about 10 per cent of W'_s using Lennard-Jones forces. EQUATION 30 is modified accordingly.

$$\lambda_x = a \cdot e^{0.9 W'_s/2kT} \tag{31}$$

If ϕ_1 is the bond energy of 3.47 Å. interatomic separation, and ϕ_2 is the bond energy for 3.00 Å. separation, the value of W'_s may be written

$$W'_s = 4\phi_1 \tag{32}$$

and the heat of evaporation may be written

$$\Delta H = 3\phi_1 + 3\phi_2 \tag{33}$$

There is no information available on the energy ratios ϕ_1/ϕ_2 other than $\phi_1/\phi_2 = p > 1$. Combining EQUATIONS 33, 31, and 32, it may be written that

$$\lambda_x = a \cdot \exp. \left\{ \frac{3.6p}{6(p+1)} \cdot \frac{\Delta H}{RT} \right\} \tag{34}$$

Introducing the values $\lambda_x = 2.5 \times 10^{-3}$ cm., $a = 3.00$ A., $\Delta H = 15{,}000$ cal./mol into EQUATION 29 and solving for p, it is found that

$$p = \phi_1/\phi_2 = 1.15 \tag{35}$$

Platelet Growth

The analysis of platelet growth follows the same general pattern as the treatment of whisker growth. By the nature of geometric differences in the form of the growing crystal, the detailed treatments differ considerably.

Platelet thickness. To estimate the thickness of a platelet from its average deflection in Brownian motion, an assumption must be made as to the dimensions of the platelet-glass interface. As an approximation, the interface is taken as a square the length of whose edge equals the thickness of the platelet.

The differential equation for the deflection curve of a bent beam is written

$$EI \frac{d^2y}{dx^2} = M \tag{36}$$

where y is the deflection at any point x along the beam, E is Young's modulus, I is the moment of inertia, and M is the bending moment.

Since a platelet is a beam of constant thickness τ but of increasing width $b(x)$ with increasing x, where $x = \tau$ at the support, most of the bending occurs in the neighborhood of the support. The rhombic lateral face is replaced for ease of calculation by a triangular face supported at 1 apex and having a perpendicular height, l, equal to the length of the diagonal of the original rhombohedron.

To calculate the energy expended in bending the platelet through an angle, θ, the deflection curve EQUATION 36 is solved for a concentrated load, F, applied at the distance, l, from the support, as in FIGURE 7.

The moment of inertia is given by

$$I = \frac{\tau^3 \tan \alpha}{6} \tag{37}$$

and the bending moment by

$$M = -F(l - x) \tag{38}$$

Combining EQUATIONS 36, 37, and 38, it is seen that

$$\frac{E\tau^3 \tan \alpha}{6} \frac{d^2y}{dx^2} = -F\left(\frac{l}{x} - 1\right) \tag{39}$$

Integrating EQUATION 39 and applying the boundary condition $dy/dx = 0$ for $x = \tau/(2 \tan \alpha)$, it follows that

$$\frac{dy}{dx} = -\frac{6F}{E\tau^3 \tan \alpha} l \ln \frac{2x \tan \alpha}{\tau} - x + \frac{\tau}{2 \tan \alpha} \tag{40}$$

The deflection, $\theta_{\text{max.}}$, at $x = l$ is obtained from EQUATION 40 with the approximations that $dy/dx = \theta$ and $l \gg \tau$,

$$F = -\frac{E\tau^3 \tan \alpha}{6l \ln \dfrac{2l \tan \alpha}{\tau}} \cdot \theta_{\text{max.}} \tag{41}$$

The potential energy, U, of a bent beam is given by

$$U = \frac{E\tau^3 \tan \alpha}{12l \ln \dfrac{2l \tan \alpha}{\tau}} \cdot \theta_{\text{max.}}^{\;2} \tag{42}$$

If θ is the average angular deflection of a platelet in Brownian motion, and it is approximated that $\overline{\theta^2} = \bar{\theta}^2$, it may be written that

$$\frac{E\tau^3 \tan \alpha}{12l \ln \dfrac{2l \tan \alpha}{\tau}} \theta_{\text{max.}}^{\;2} = kT \tag{43}$$

and the platelet thickness is given by

$$\tau = \left\{\frac{12lkT \ln \dfrac{2l \tan \alpha}{\tau}}{E\theta_{\text{max}}^{\;2} \tan \alpha}\right\}^{1/3} \tag{44}$$

The numerical solution of EQUATION 44 involves a preliminary assumption for the value of τ. The calculated value of τ is very insensitive to variation in the assumed value. Using the values $l = 3 \times 10^{-2}$ cm., $T = 310°$ K., tan $\alpha = 0.70$, $E = 10^{11}$ dynes/cm.^{2}, $\theta = 0.03$, and $\tau = 3 \times 10^{-6}$ cm., it is found that

$$\tau_{\text{calc.}} = 12 \times 10^{-6} \text{ cm.}$$

If the first approximation of $\tau_{\text{calc.}}$ is introduced into the left side of EQUATION 44, the second approximation in $\tau_{\text{calc.}}$ differs by only 10 per cent from the first approximation.

Growth rate. Volmer and Estermann[13] established that vapor molecules impinged upon the large lateral faces and diffused in the self-adsorbed layer to the platelet edges where incorporation into the crystal occurred. Since diffusion occurs on the lateral faces, it is assumed that these faces carry no growth sites.

The rate of advance $\dot{x}$ of a growing edge is given by

$$\dot{x} = \frac{2\lambda_s\{P - P_o(\tau, T)\}}{\rho\tau}\sqrt{\frac{m}{2\pi kT}} \tag{45}$$

where λ_s is the mean free path of surface diffusion, ρ is the density of solid mercury, τ is the platelet thickness, P is the pressure of the supersaturated vapor, and $P_o(\tau, T)$ is the vapor pressure of a platelet of thickness, τ, at a temperature, T. The function $P_o(\tau, T)$ is related to the vapor pressure, $P_o(T)$ at temperature, T, by the equation

$$P_o(\tau, T) = P(T)\cdot\text{exp.}\left(\frac{2\gamma M}{\rho\tau RT}\right) \tag{46}$$

where γ is surface free energy of solid mercury, and M is its atomic weight. Introducing the numerical values $\gamma = 500$ ergs/cm.^{2}, $\rho = 13.6$ gm./cm.^{3}, $M = 200$ gm., and $T = 210°$ K., it is seen that

$$P_o(\tau, 210°) = P_o(210°)\cdot e^{(8.41\times 10^{-7}/\tau)} \tag{46a}$$

EQUATION 17 is valid if the growth rate $\dot{x}$ is calculated from the rate of vapor impingement only where surface diffusion is neglected and it is assumed that $P \gg P_o\,(\tau, T)$. A numerical estimation of $\dot{x}_i$ for $P = 7 \times 10^{-2}$ dynes/cm.^{2}, $\rho = 13.6$ gm./cm.^{3}, and $T = 298°$ K. yields

$$\dot{x}_i\text{ (calc.)} = 1.8 \times 10^{-7}\text{ cm./sec.}$$

The empirical value of lateral growth rate of mercury platelets is

$$\dot{x}\text{ (obs.)} = 2.5 \times 10^{-4}\text{ cm./sec.}$$

The observed growth rate is thus 720 times too large to be accounted for by impingement without surface diffusion.

Combining EQUATIONS 17 and 45, the ratio, R, of growth rates with diffusion and without diffusion may be written

$$R = \frac{2\lambda_s}{\tau}\left[1 - \frac{P_o(\tau, T)}{P}\right] \tag{47}$$

The combination of EQUATIONS 46a and 47 with the experimental pressure of supersaturated vapor $P = 1600$, $P_o(T)$ yields

$$R = \frac{2\lambda_s}{\tau}\left[1 - \frac{\text{exp.}\left(\dfrac{8.41 \times 10^{-7}}{\tau}\right)}{1600}\right] \tag{48}$$

The value $\lambda_s = 0.025$ mm. has been calculated from the growth kinetics of mercury whiskers.[9] The value $\tau = 12 \times 10^{-8}$ cm. has been calculated in the preceding section. The numerical solution of EQUATION 46a gives

$$R_{\text{calc.}} = 12{,}000$$

compared to the observed value, $R = 720$. The calculated value of R is quite sensitive to variation of τ. If the value $\tau = 11.6A$ is introduced instead of $\tau = 12.0A$, the calculated value of R agrees exactly with the observed value of R. The presently calculated thickness is consistent with the growth kinetics and the intensity of Brownian motion. The thickness $\tau = 300A$ estimated by Volmer and Estermann[15] is such that Brownian motion would not occur.

Since platelets are always connected at a corner, the sites of growth can be localized at 2 of the edge faces. In FIGURE 6, it can be seen that the advance of edges A and B would destroy the point attachment and cause a line attachment in edge faces C and D. Since all bounding faces of a platelet are presumably {100} planes, it is postulated that screw-dislocation components are emergent on faces C and D. This postulate accounts for the advance of these faces in the absence of growth of faces A, B, and the lateral faces.

Two-dimensional nucleation as a growth mechanism is not operative under these experimental conditions. The crystals were grown at supersaturation ratios of 1600:3000. For comparison, the critical supersaturation ratio for a nucleation rate of 1 layer/cm.^{2}/sec. is 4,000,000. For edgewise growth at the observed rate of 2×10^{-4} cm./sec., a supersaturation ratio of $\alpha \sim 10^{10}$ would be required. The values of a supersaturation ratio are obtained by solving the nucleation rate (EQUATION 9) using numerical values $B = 10^{20}$ sec.$^{-1}$, $\gamma = 500$ ergs/cm.^{2}, $a = 3 \times 10^{-8}$ cm., $M = 200$ gm., $\rho = 13.5$ gm./cm.^{3}, and $T = 210°$ K.

Mechanism of platelet growth. It is possible to deduce a mechanism of mer-

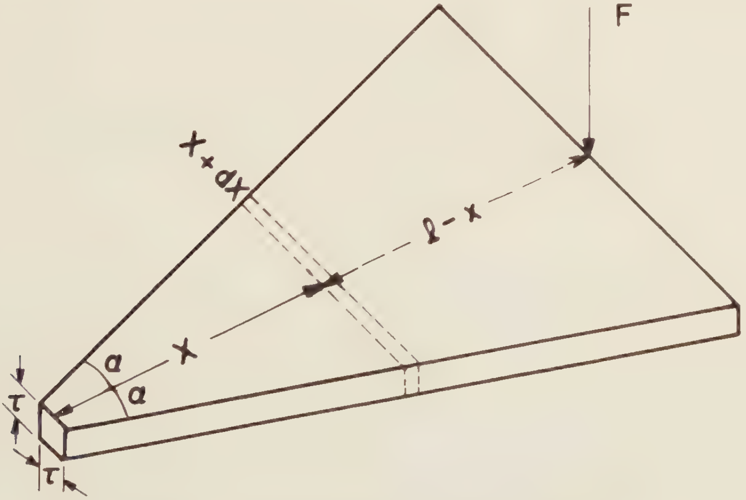


FIGURE 7. The bending load of a mercury platelet.

cury platelet growth consistent with the observed growth kinetics. Mercury whiskers are presumed to nucleate on tiny crystalline regions on a glass surface that presents screw-dislocation ends. The dislocation is transposed to a screw dislocation in the mercury crystallite, and the crystallite grows from the glass surface as a whisker. The necessary condition is that the supersaturation be insufficient to give an appreciable 2-dimensional nucleation rate on the whisker surface. The screw axis is assumed to be a [100] direction, the whisker is rhombic in cross section and is bounded by rhombohedral {100} planes. The {100} planes are most closely packed and have the lowest surface free energy.

It has been postulated for the growth of potassium halide platelets from aqueous solution[23] and *p*-toluidine platelets[24] from vapor condensation that lateral growth involves a set of cross-screw dislocations. A crystal bearing a set of crossed screw dislocations is actually a bicrystal with a small angle twist boundary. Such a crystal growing by the screw-dislocation mechanism must grow laterally in all directions. No matter how much the crystal grows, the edges must always present screw-dislocation ends.

As was shown in the preceding section, mercury platelets grow laterally only in 2 crystallographic directions. It is postulated that if the mercury nucleus forms on a glass crystallite bearing a screw dislocation, and with a [110] screw axis instead of a [100] screw axis, a platelet habit will result. A pair of rhombohedral {100} planes are parallel to the [110] direction. Since a pair of rhombohedral {110} planes are also parallel to the [110] screw axis, it is supposed that the surface energy of {100} planes is less than the surface free energy of {110} planes. Analytically, it may be written that

$$\frac{\gamma_{100}}{\cos 36^\circ} < \gamma_{110}$$

and since platelets are attached at the 72° corner, not the 108° corner (see FIGURE 6), that

$$\frac{\gamma_{100}}{\cos 54^\circ} > \gamma_{110}$$

where the superscripts refer to the indices of the plane type corresponding to the surface energy. The bounds of the surface free energy ratio are given numerically:

$$0.59 < \frac{\gamma_{100}}{\gamma_{110}} < 0.81$$

Growth proceeds by impingement of mercury atoms from the gas phase upon the crystal surface, followed by surface migration over perfect surfaces to the growth sites in a pair of edge faces. In the neighborhood of a screw-dislocation end, the surface supersaturation is determined by the vapor pressure of the platelet, $P_s(\tau, T)$. Far from a growth site, the surface supersaturation is determined by the pressure, P, of supersaturated vapor. Thus a platelet must reach a critical length before it can thicken. The supersaturation is insufficient to cause thickening by 2-dimensional nucleation, and thickening occurs by intermediation of the glass-mercury step at highest supersaturations in the adsorbed layer; that is, far from a growth site.

Mechanical Properties

The bending of a thin platelet attached to a support at its corner is most severe in the immediate neighborhood of the support. The local maximum strain, Σ, in bending is given by

$$\Sigma = \frac{\tau}{2R(x)} \tag{49}$$

where τ is the platelet thickness and $R(x)$ is the radius of curvature. To a first approximation

$$\frac{1}{R(x)} = \frac{d^2y}{dx^2} \tag{50}$$

and it may be written that

$$\Sigma = \frac{\tau}{2}\frac{d^2y}{dx^2} \tag{51}$$

Combining EQUATIONS 5 and 7, it is seen that

$$\frac{d^2y}{dx^2} = \frac{\theta_{\max}\left(\frac{1}{x} - \frac{1}{l}\right)}{\ln\frac{2l\tan\alpha}{\tau}} \tag{52}$$

The maximum strain, Σ, is found for $x = \tau/(2\tan\alpha)$ and may be expressed analytically by combination of EQUATIONS 19, 20, and 22

$$\Sigma = \frac{\theta_{\max.}\cdot\tan\alpha}{\ln\frac{2l\tan\alpha}{\tau}} \tag{53}$$

Introducing numerical values $\theta_{\max.} = 0.03$, $l = 3 \times 10^{-2}$ cm., $\tau = 10^{-7}$ cm. and $\alpha = 36°$, it is found that

$$\Sigma = 0.002$$

The maximum strain of a platelet in Brownian motion is 0.2 per cent, which exceeds the elastic limit of an ordinary single crystal of mercury by at least twentyfold. This calculation strongly suggests that the mercury platelets have the high strengths characteristic of the whisker habit.

Platelet versus Whisker Nucleation

The parent nuclei leading to platelet formation and whisker formation are postulated to differ only in the crystallographic direction of the screw axis. A platelet nucleus is believed to form with a {110} face parallel to the glass crystallite substrate, and a whisker nucleus is believed to form with a $\{100\}$ face parallel to the glass substrate.

Both crystal habits have large and approximately equal growth velocities, so that the absence of a particular habit is evidence for the lack of nucleation of the parent nucleus in question. It is not surprising that the nucleation event may favor one crystallography or another, with a small variation in deposition conditions. Brenner,[25] for example, has observed [110], [111], and [100] axial directions for copper whiskers grown by vapor-phase reduction. The absence of any detailed information of surface energies involved precludes definitive discussion of the nucleation event.

Corroborative Evidence for Growth Mechanism

Experimental estimation of critical supersaturation. It is evident that the conditions for the growth of mercury platelets and whiskers are not restricted to this substance, but are universally valid for the growth of crystalline whiskers and platelets. The basic postulate states that a nucleus bearing a single screw dislocation will grow in the direction of the screw axis at constant cross section at supersaturations below the critical value for an appreciable rate of 2-dimensional nucleation. Similarly, a crystallite bearing a planar set of crossed screw dislocations will grow as a platelet under similar conditions. The mechanism is not limited to vapor deposition but may occur in any growth process where the screw dislocation is operative.

Whiskers have been grown[26] of cadmium, zinc, silver, and cadmium sulfide at controlled supersaturations. For each substance a critical supersaturation was found, above which massive crystal growth occurred, and below which whisker and platelet growth occurred. These observations are rationalized by assuming that the critical measured supersaturation corresponds to the critical supersaturation for 2-dimensional nucleation. The theoretical supersaturation for 2-dimensional nucleation, $\alpha^*_{\text{calc.}}$, may be calculated from EQUATION 20. In TABLE 2 the calculated critical supersaturations are compared with the experimentally estimated upper limit, $\alpha^*_{\text{meas.}}$, for the growth of whiskers.

The above agreement between $\alpha^*_{\text{meas.}}$ and $\alpha^*_{\text{calc.}}$ is considered to be very good. The calculated value, $\alpha^*_{\text{calc.}}$, is very sensitive to changes in growth temperature. Since the surface free energy should be relatively constant with temperature, the calculated value, $\alpha^*_{\text{calc.}}$, should increase rapidly with decreasing growth temperature.

TABLE 2

Substance	$\alpha^*_{\text{calc.}}$	$\alpha^*_{\text{meas.}}$	Temp. °C.	$\rho\ \left(\frac{\text{g}}{\text{cm.}^3}\right)$	$\sigma\ \left(\frac{\text{ergs}}{\text{cm.}^2}\right)$	$\alpha \times 10^8$ cm.
Cd	24	20	250° C.	8.65	630[27]	2.80[29]
Zn	7	3	350° C.	7.14	750[27]	2.47[29]
Ag	4	10	850° C.	10.50	1140†	2.04[29]
Cd S	small	≤ 2	800° C.	4.82	—	—

† Surface free energy solid Ag[28]

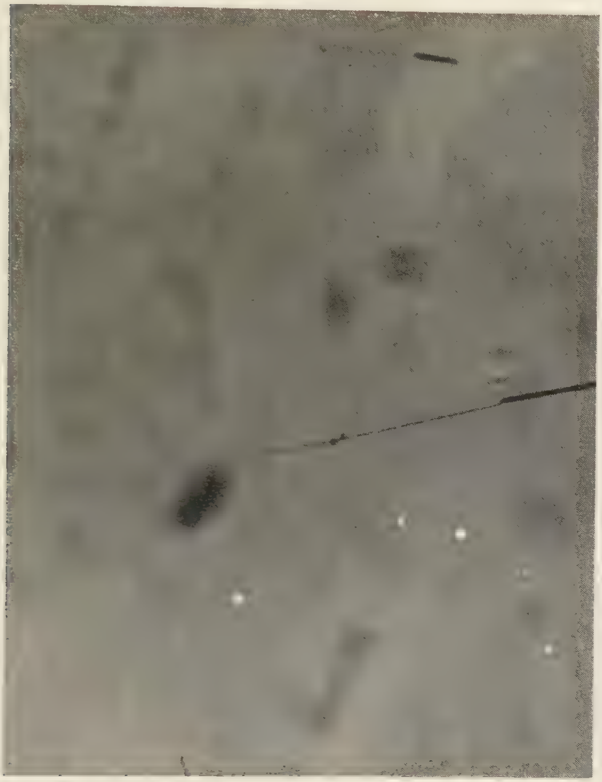


FIGURE 8. Zinc platelet growth beginning as "butterfly wings." ×30.

It appears from the preceding evidence that the critical condition for whisker growth proposed to account for mercury whiskers and platelets is generally valid for crystalline whiskers and platelets.

Growth artifacts. In a study of the growth of zinc whiskers[30] in the presence of an inert foreign gas it was possible to grow a profusion of long, thin zinc whiskers.

In many instances, whiskers come in contact with one another during growth. At the whisker junctions, platelets of zinc[31] began to grow as shown in FIGURES 8 to 10. The platelet growth began as "butterfly wings" (FIGURES 8 and 9), with growth filling in the 2 acute angles at early stages. When growth occurred for a longer time, as judged by platelet size, the entire junction was filled in with platelet growth.

In one instance, shown in FIGURE 10, a butterfly wing grew into a whisker that was nearly perpendicular to the wing. The platelet began to grow in thickness. The other wing of the same butterfly continued to grow as a plate.

Many examples were seen in which a straight segment of whisker extended from its site of growth to an interfering crystal. These sections were many times shorter than the average length of unimpeded whiskers.

FIGURE 9. Zinc platelet growth beginning as "butterfly wings." ×30.

When 2 whiskers cross at an angle to one another, the grain boundary so formed is a twist boundary and is defined by a set of crossed screw dislocations. Such a boundary is shown in FIGURE 11, after Frank.[32] Experimentally, platelet growth occurred from a parent crystal region bearing a set of crossed screw dislocations. This is direct evidence for the reality of the mechanism of platelet growth. Conversely, the whisker existing in the vicinity of the plate implies the absence of sites of growth, at least locally on the whisker.

In FIGURE 10, a platelet has met a nearly perpendicular whisker and grown around it. The grain boundary between whisker and platelet is defined in part by a set of screw dislocations, since there is a component of twist. The screw component normal to the platelet causes thickening. Conversely, the absence of thickening in the other wing implies the absence of screw dislocations with a component normal to the surface of the platelet.

The observation of short, straight sections of whiskers between the site of growth and the interfering crystal can be accounted for only by tip growth such as is postulated with the screw-dislocation growth mechanism. A whisker growing at its tip would immediately cease growth if the tip ran into a second crystal and would give a straight section. A whisker growing at its base

FIGURE 10. "Butterfly wing" that has grown into a whisker nearly perpendicular to the wing. ×30.

would continue to grow, and it would form an arc between the base of the whisker and the interfering crystal. A base-grown whisker would form only a straight segment if growth ceased at the moment of interference. While this might happen on a rare occasion, the large number of straight segments observed supports the tip-growth hypothesis. Since neighboring whiskers with free ends had much greater lengths than the whisker segments, it is highly probable that the supersaturation did not diminish at the base of the whisker and thus cause cessation of growth.

Physical Properties

Elastic properties. The properties of real crystals reflect not only the crystal composition but also the defect structure. Since the platelets and whiskers described in the present discussion are believed to be particularly free of dislocations, it is expected that they should differ markedly in some properties from ordinary crystals.

The mechanical strength of real crystals is a thousandfold less than the expected theoretical strengths[33] of perfect crystals. The elastic limit of most

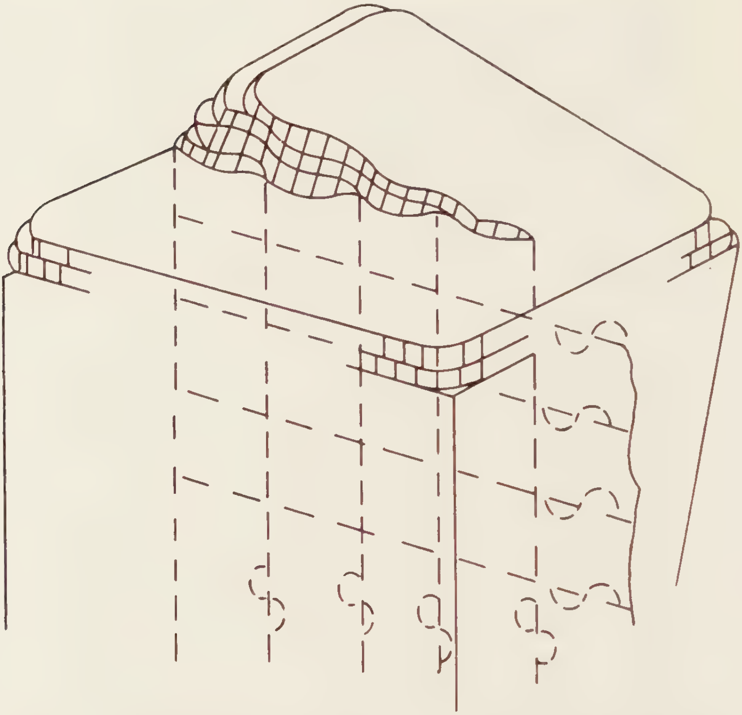


FIGURE 11. Diagram of "twist" boundary—a crossed grid of screw dislocations.

single crystals of metal occurs at strains of 0.001 to .01 per cent, whereas the estimated elastic limit for a perfect crystal is about 3 per cent. Whiskers of several materials tested in tension were found to exhibit the elastic limits expected for perfect crystals. In TABLE 3, the elastic limits for several materials are compared to the values for ordinary single crystals.

It should be emphasized that, while the high elastic limits of crystalline whiskers are consistent with the proposal of near perfection, the elastic properties are not proof of structural perfection.

Evaporation kinetics. A study of the evaporation kinetics of platelets of *p*-toluidine[36] has shown that evaporation does not occur at an appreciable rate

TABLE 3

Material	Whisker axis	Elastic limit whiskers	Elastic strain	Elastic limit ordinary crystals
		p.s.i.		*p.s.i.*
Iron[34]	[111]	1,900,000	4.8%	5,000
Copper[34]	[111]	440,000	1.6%	150
Silver[34]	[100]	250,000	4.0%	100
Zinc[30]	[1000]	56,000	1.1%	100
Silicon[35]	[111]	410,000	2.0%	—

until a critical undersaturation is attained in the vapor phase. The behavior is explained readily by assuming that the lateral platelet faces can evaporate only by a 2-dimensional nucleation mechanism.

Crystal recovery. If a copper whisker is kinked by bending beyond its elastic limit, the whisker will straighten out spontaneously[37] if heated to a temperature of about 1000° C. for about 15 min. The straightened whisker recovers its high elastic strength as measured in bending.

Conclusions

A study of the growth of mercury whiskers and platelets has led to the conclusion that the growth kinetics are the consequence of near perfection of the growing crystals. An investigation of evaporation kinetics has offered confirmatory evidence as to platelet perfection. Studies of mechanical properties are consistent with the proposed near perfection but do not furnish definite proof.

The detailed structures of platelets and whiskers will have to be determined by careful X-ray examination. Without regard to structural perfection, however, it is now possible to investigate continuous changes in crystal symmetry and the consequences thereof, since an expanded range of elastic deformation is now attainable experimentally.

References

1. Gibbs, J. W. 1928. Collected Works.: 325. Longmans Green & Co. London, England.
2. Kossel, W. 1927. Nachr. Ges. Wiss. Göttingen.: 135.
3. Stranski, I. 1928. Z. physik. Chem. **136:** 259.
4. Becker, R. & W. Doring. 1935. Ann. phys. **24:** 719.
5. Frenkel, J. 1945. J. Phys. (U. S. S. R.) **9:** 3921.
6. Volmer, M. & W. Schultze. 1931. Z.physik. Chem. **156A:** 1.
7. Frank, F. C. 1949. Discussions Faraday Soc. **5:** 48, 67.
8. Verma, A. R. 1953. Crystal Growth and Dislocations. Academic Press. New York, N. Y.
9. Forty, A. J. 1951. Phil. Mag. **42:** 670.
10. Newkirk, J. B. 1955. Acta Metallurgica. **3:** 121.
11. Burton, W. K., N. Cabrera & F. C. Frank. 1951. Phil. Trans. Roy. Soc. **243:** 299.
12. Burton, W. K. & N. Cabrera. 1949. Discussions Faraday Soc. **5:** 33.
13. Volmer, M. & I. Estermann. 1921. Z. Physik. **7:** 13.
14. Langmuir, I. 1913. Physiol. Revs. **2:** 329.
15. Langmuir, I. 1914. Physiol. Revs. **4:** 377.
16. Langmuir, I. 1915. J. Am. Chem. Soc. **37:** 1139.
17. Langmuir, I. 1917. Proc. Natl. Acad. Sci. **3:** 141.
18. Sears, G. W. 1953. Acta Metallurgica. **1:** 457.
19. Sears, G. W. 1955. Acta Metallurgica. **3:** 361.
20. Sears, G. W. 1956. J. Chem. Phys. To be published.
21. Beyersdorf, K. 1952. Glas und Hochvakuum Technik. **2:** 8.
22. McKenzie, A. J. 1951. Thesis. Univ. Bristol. Bristol, England.
23. Newkirk, J. B. & G. W. Sears. 1955. Acta Metallurgica. **3:** 110.
24. Sears, G. W. Growth of *p*-toluidine. Unpublished data.
25. Brenner, S. S. 1956. Acta Metallurgica. **4:** 62.
26. Sears, G. W. 1955. Acta Metallurgica. **3:** 367.
27. Hogness, T. R. 1921. J. Am. Chem. Soc. **43:** 1621.
28. Funk, E. R., H. Udin & J. Wulff. 1951. Trans. Am. Inst. Mining Met. Engrs. **191:** 1206.
29. Barrett, C. S. 1943. Structure of Metals. 1st ed. McGraw-Hill. New York, N. Y.

30. Coleman, R. V. & G. W. Sears. Growth of Zinc Whiskers. Acta Metallurgica. To be published.
31. Sears, G. W. & R. V. Coleman. Growth mechanism of near-perfect crystals. J. Chem. Phys. To be published.
32. Frank, F. C. 1949. Discussions Faraday Soc. **5:** 33.
33. Bragg, L. & W. M. Lomer. 1949. Proc. Roy. Soc. London. **A196:** 71.
34. Brenner, S. S. Tensile Strengths of Whiskers. To be published.
35. Eisner, R. L. 1955. Acta Metallurgica. **3:** 419.
36. Sears, G. W. 1956. J. Chem. Phys. **24:** 868.
37. Brenner, S. S. & R. L. Morelock. 1956. Acta Metallurgica. **4:** 89.

THE PHYSICAL PROPERTIES OF MERCURY IMPORTANT IN ELECTRONICS

By Erwin F. Lowry
Sylvania Electric Products Inc., Salem, Mass.

The physical properties of mercury are uniquely suited to the demands of gaseous electronics. No other element possesses characteristics so peculiarly and eminently suited to the requirements of a variety of electronic devices. Actually we owe to mercury the very existence of a large number of extremely important electronic appliances. The mercury-pool rectifier, the ignitron, hot-cathode rectifiers and thyratrons, the Cooper Hewitt lamp, fluorescent and germicidal lamps, photo-copying lamps, and the increasingly popular high-pressure mercury lamps are all dependent on the unique physical properties of this singular element. The physical properties in which we are particularly interested in this connection are atomic weight, vapor pressure versus temperature, and the energy levels for excited atoms.

Mercury is the only metal that is liquid at 0° C. and that has an appreciable vapor pressure at, or slightly above, room temperature. It has an atomic weight of 200.6, with a resulting very low ionic-drift velocity in an electric field. The energy levels of excited mercury atoms are strategically located, to say the least. As will be shown, the energy levels of mercury give rise to radiation at wave lengths of extreme importance. Furthermore, its ionization potential (10.4 v.) is lower than that of the rare gases, which is a very useful quality in devices such as the fluorescent lamp, where argon is used with mercury.

The mercury-pool rectifier was the first important application of mercury in an electronic device. This rectifier came into important commercial use about 50 years ago under the able guidance of such men as Hewitt, Steinmetz, and Conrad. The source of electron emission in this rectifier is the well-known cathode spot on the surface of the mercury pool. This emission is tremendous, being of the order of 4000 amp./cm.^{2} with a cathode fall of potential of only 7 v.[1] The mechanism of cathode-spot emission is still the subject of considerable discussion.[2] It seems evident that it is only partially thermionic. The best measurements of the temperature of the cathode spot are only slightly over 2000° C., and this value is too low to account for the copious electron release observed.

Since the mass of the mercury ion is very high compared to that of the electron, and its drift velocity is correspondingly low, more than 90 per cent of the arc current is carried by electrons. Langmuir and Mott-Smith[3] have estimated that the electron current in low-pressure arcs may be several hundred times the ion current. Since the chief function of the mercury ion in the discharge is to neutralize the electron space charge, and since the ratio of mobilities of mercury ions and electrons is of the order of 1 to 600, it turns out that 1 mercury ion can neutralize the space charge for hundreds of electrons. An immediate and very important consequence of this situation is that in an arc-discharge device such as the mercury rectifier a low pressure of mercury vapor is quite adequate to neutralize the electron space charge and permit a high current-carrying capacity. This in turn leads to the very important consequence that such rectifiers may be used on very high voltages without "backfires" or breakdown during the inverse half cycle.

Paschen discovered in 1889 that the sparking potential is a function of the product of pressure and gap length only. This relation for mercury vapor is shown in FIGURE 1 when breakdown voltage is plotted against pd, where p is in millimeters of mercury, and d is in centimeters. Since the working pressure in a mercury-pool rectifier may be only a few microns, these rectifiers may be operated at several thousands of volts without serious trouble with backfires, provided adequate precautions are taken to prevent the formation of cathode spots on the anodes. KDKA, Pittsburgh, Pa., the pioneer radio broadcast station in the United States, operated its 50-KVA transmitter for a considerable period on the DC power furnished by multiple-anode mercury-pool rectifiers.

The ignitron widely used today in heavy DC welding applications is a particular type of mercury-pool rectifier in which a special device is used for starting and maintaining the arc. Slepian and Ludwig[4] found that a small rod of relatively high resistance material, such as boron carbide, when partially immersed in the mercury pool will form and maintain a cathode spot when current is passed from the rod to the pool. A peak current of about 3 amp. at 100 v. is usually required to insure ignition. The ignition time is usually of the order of 100 μsec. This time is controlled by another mercury-vapor device known as a thyratron. The thyratron is a hot-cathode rectifier to which has been added a grid structure for control purposes.

In the hot-cathode rectifier, as in the mercury-pool rectifier, the function of the mercury vapor is to neutralize the electron-space charge and thus, in effect, move the anode very close to the cathode. The low ionization voltage and slow drift velocity of mercury are as useful here as they are with the mercury-pool rectifier. A thermionic cathode, usually of the oxide-coated type, has replaced the mercury-pool cathode; consequently, the only function of the mercury vapor is to provide high conductivity. Enough mercury vapor must be present for this purpose and yet not so much that inverse breakdown is too low. The tube designer takes care of this situation by arranging that the coolest spot on the tube during normal operation will be between 25° C. and 90° C. When the mercury-vapor pressure is limited to about 10 μ by this means, hot-cathode rectifiers may be operated at an inverse peak voltage as high as 50,000 v. In fact, it has been common practice to test hot-cathode rectifiers for use in radio transmitters at 50,000 v., although they are usually rated at 20,000 v. or less.

The heavy atomic weight and low mobility of mercury ions has one disadvantage, and that is a long deionization time (of the order of 1 to 10 msec.). This time may be varied somewhat by changing electrode spacings and by similar schemes, but mercury is definitely not well-suited for use in electronic tubes at high frequencies. For this reason, hot-cathode rectifiers and thyratrons are mostly single-anode devices, particularly at high voltages. Hydrogen

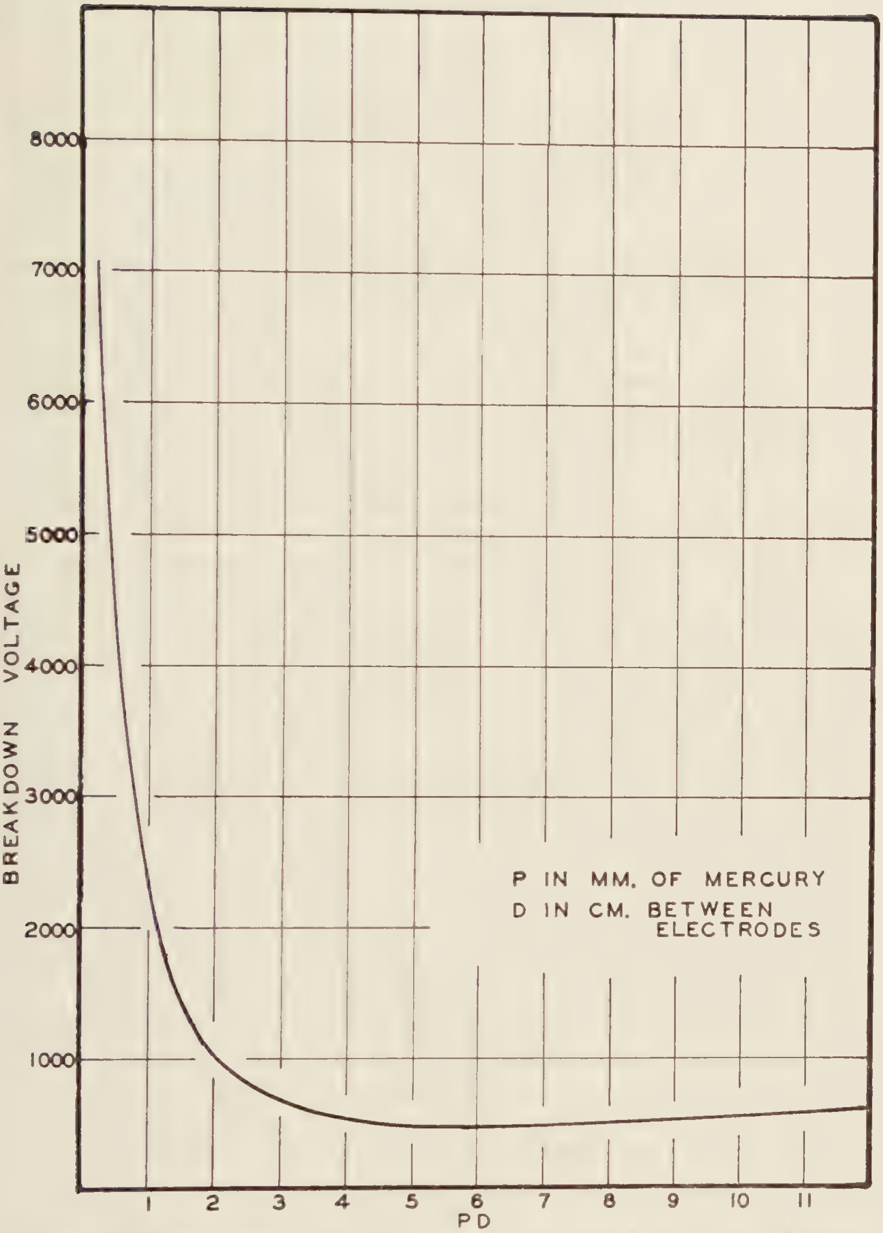


FIGURE 1. Sparking potential in mercury vapor as a function of the pressure and distance between electrodes.

must be used as fill gas in modern pulse tubes at microwave frequencies because hydrogen ions have about 20 times the mobility of mercury ions and therefore are able to reach the tube walls, where most of the deionization occurs, in much shorter time.

FIGURE 2 is a plot of mercury-vapor pressure as a function of temperature. On this plot are indicated the operating temperatures from which are derived the useful mercury-vapor pressures for a number of the more important electronic devices that utilize mercury vapor for their operation. The hot-cathode rectifiers and thyratrons usually operate at mercury pressures of between 2 and 100 μ. Mercury-pool rectifiers also operate within this pressure range. Some rectifiers are designed to operate at pressures as high as 1 mm. At this operating pressure they will not withstand peak inverse voltages of more than 500 to 600 v., but they have a very low arc voltage in the forward or current-carrying direction. This low arc voltage is due, at least in part, to the metastable levels of mercury. These metastable levels at 4.7 and 5.4 v., respectively, have long lifetimes, so there is ample opportunity for mercury atoms, excited to one of the metastable levels, to be raised further to ionization by cumulative ionization. As a result, the arc voltage in such discharge devices may be only slightly in excess of the resonance potential.[5]

FIGURE 2 also shows the pressure range involved in various types of discharge lamps. Fluorescent and germicidal lamps are operated at the lowest pressures—5 to 10 μ. This is the range of pressures at which the greatest production of resonance radiation is delivered. The old Cooper Hewitt lamp operated at 100 μ, which is still low pressure, but one at which a greater output of visible radiation is available. Modern high-efficiency mercury lamps operate at from 1 to 2 atmospheres pressure, and some water-cooled capillary lamps are operated at pressures as high as 200 atmospheres or more. Nearly all mercury lamps contain a low pressure of a gas, such as argon, to permit easy starting at room temperature, where the mercury pressure is too low to serve in starting or operating the lamp.

Regarding the energy-level of mercury,[6-8] FIGURE 3 is a somewhat simplified diagram showing the levels of particular importance to electronic applications. First and foremost is the resonance level at 4.86 v. Electrons returning from this level to the ground state cause radiation of the 2537 Å. ultraviolet line. This is the radiation that is utilized by fluorescent and germicidal lamps. When the mercury-vapor pressure is about 6 μ, between 55 and 60 per cent of all the energy input to the discharge is radiated in this 1 line.

In close energy relation to the first resonance lines are the 2 metastable levels at 4.66 and 5.43 v., respectively. Since these levels have a lifetime of the order of 1 msec., compared to the lifetime of about 10^{-8} sec. for other excited atoms, the probability of further collisions is comparatively large, and it turns out that the metastable levels play an important role in the phenomenon of cumulative ionization. As shown in the diagram, the metastable level at 5.43 v. is responsible for the important triplet at 365 mμ, as well as for the green line at 546 mμ. The 365-mμ radiation is the black light that is so popular for fluorescent signs, inspection devices, and prospectors' kits, since there are a large num-

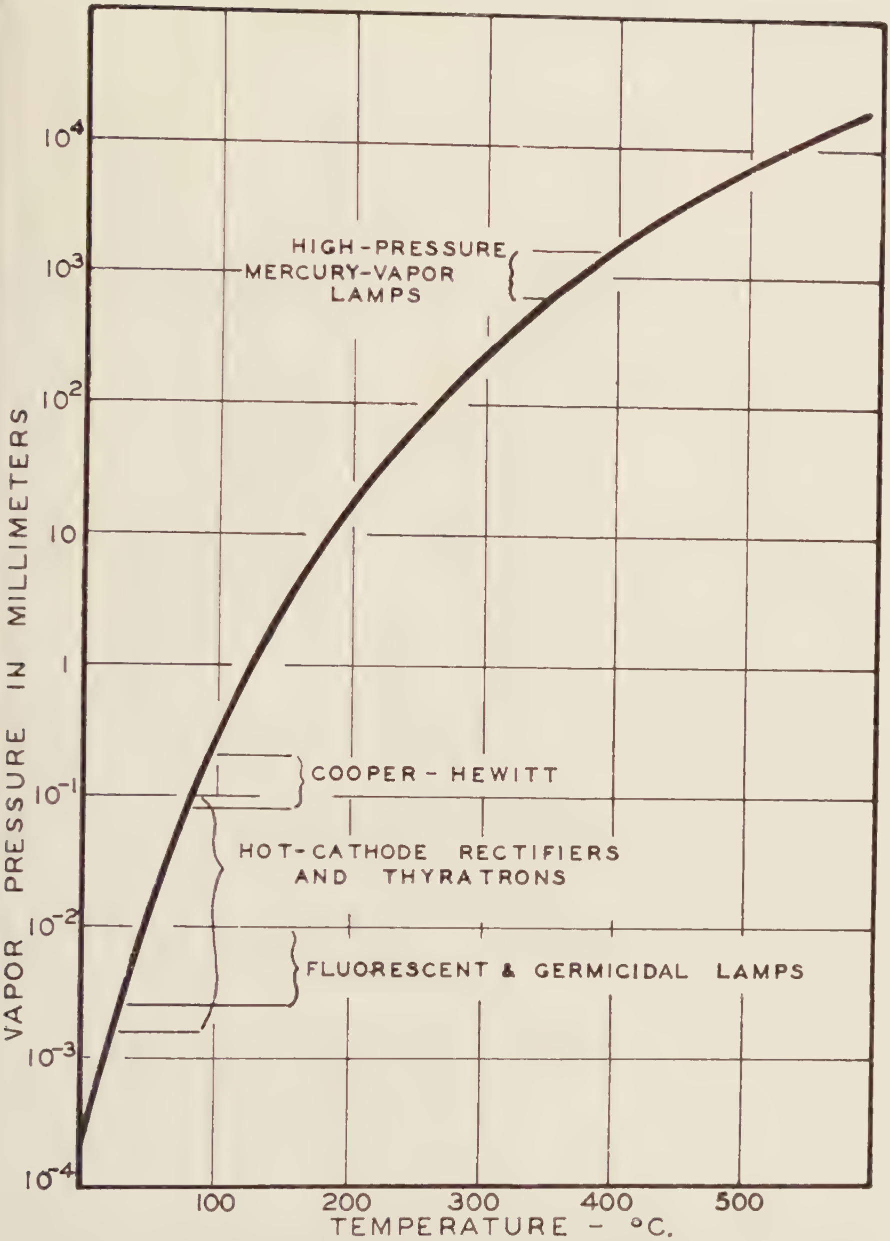


FIGURE 2. Mercury-vapor pressure as a function of its temperature. The useful pressure and temperature ranges for the various electronic devices are indicated.

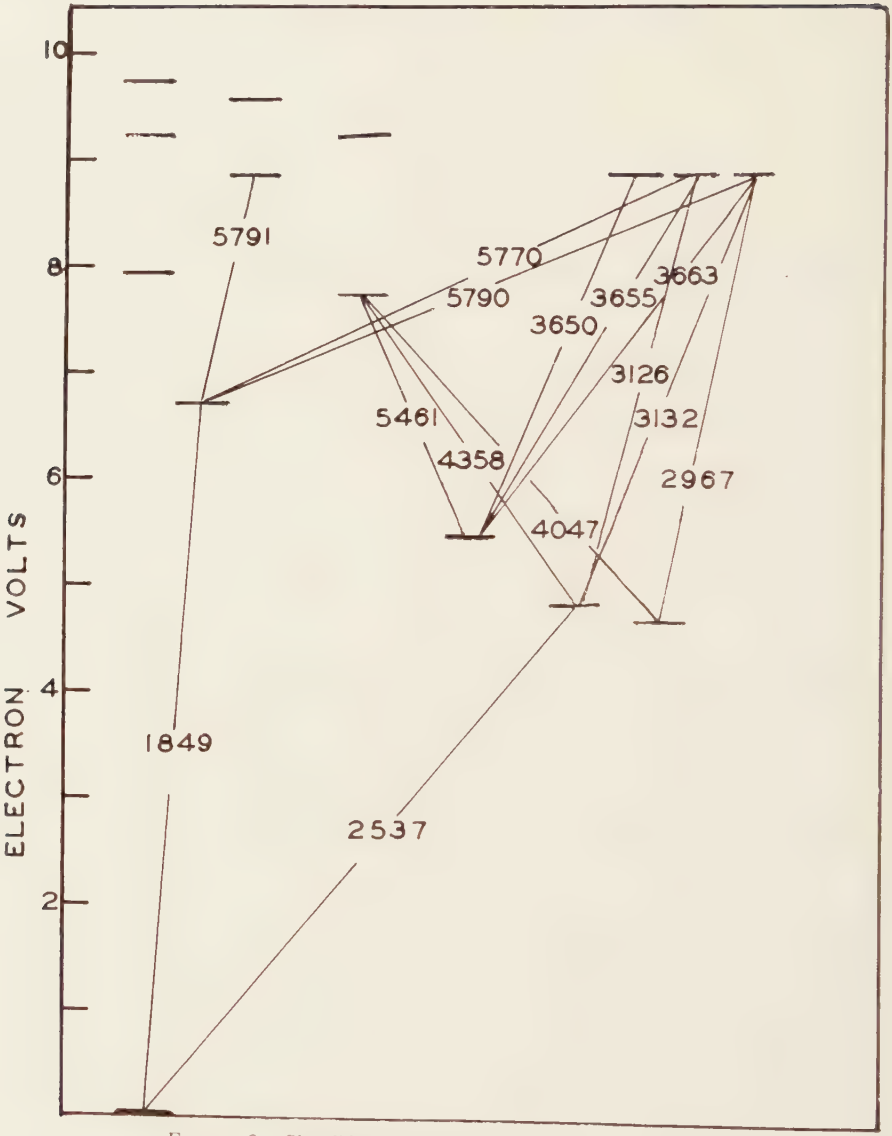


FIGURE 3. Simplified energy-level diagram for mercury.

ber of minerals and classes of phosphors that respond to radiation of this wave length. The 5461 Å. line is the wave length now being used extensively as a standard of length for interferometry. Mercury isotope 198 is used in lamps made for this purpose.

The second resonance potential of mercury is at 6.7 v. and is responsible for the 1849 Å. line that is of considerable importance as the ozone-producing radia-

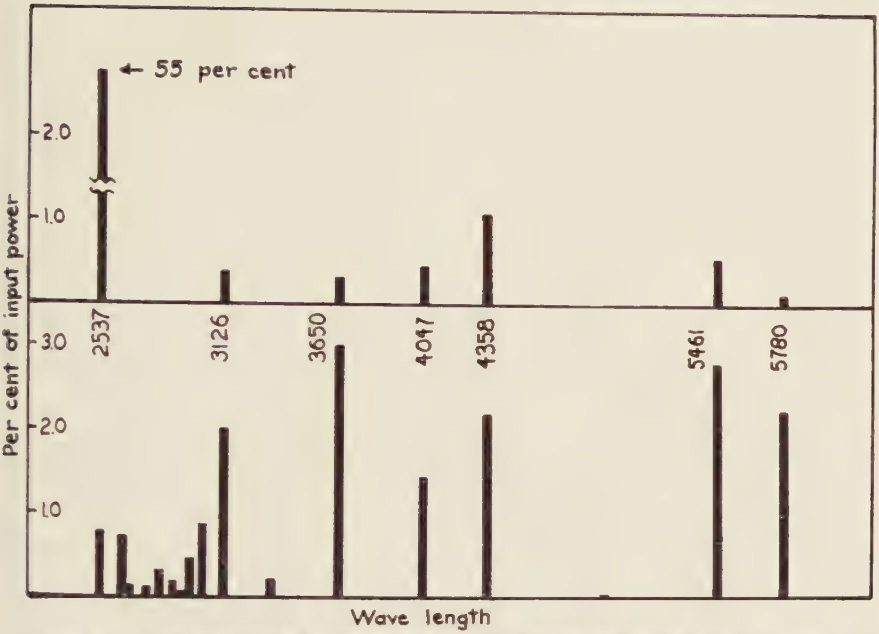


FIGURE 4. Block diagram of the relative energy contained in the principal lines of the mercury spectrum. The upper diagram shows the lines emitted at low pressures, and the lower diagram shows the lines emitted at high pressures (1 to 2 atmospheres).

tion. This ozone production is widely used in many modern devices to reduce mold growth and to eliminate objectionable odors. Electrons from the 8.8 levels falling into this resonance level are responsible for the yellow lines of the mercury spectrum at 578 mμ. The lines at 310 mμ are in the erythemal region and are important in sun lamps, and as a source of part of the useful radiation of photochemical lamps.

The visible lines of particular importance are 4 in number, at 405, 436, 546, and 580 mμ, respectively. In lamps operating at 1 atmosphere or above, these lines are emitted at sufficiently high intensities to give a lamp efficiency of about 50 lumens per watt.

FIGURE 4 presents a reasonably good picture of the situation arising in mercury discharges at low and at high pressures. The principal mercury lines emitted by low-pressure discharges are represented in the upper diagram. Here, as mentioned previously, at least 55 per cent of the total input energy to the discharge is released or emitted as the first resonance radiation at 2537 A. The other lines are relatively very low in intensity. When the pressure is raised to approximately 1 atmosphere, by increasing the energy input or by heating the discharge device by some other means, the situation changes completely. The 2537-resonance radiation decreases to about 1 per cent, while the longer wave lengths become increasingly important. The erythemal lines at 310 mμ and the near ultraviolet line at 365 mμ have increased severalfold, as have the visible lines. As mean free paths decrease with increasing pressure, and as the

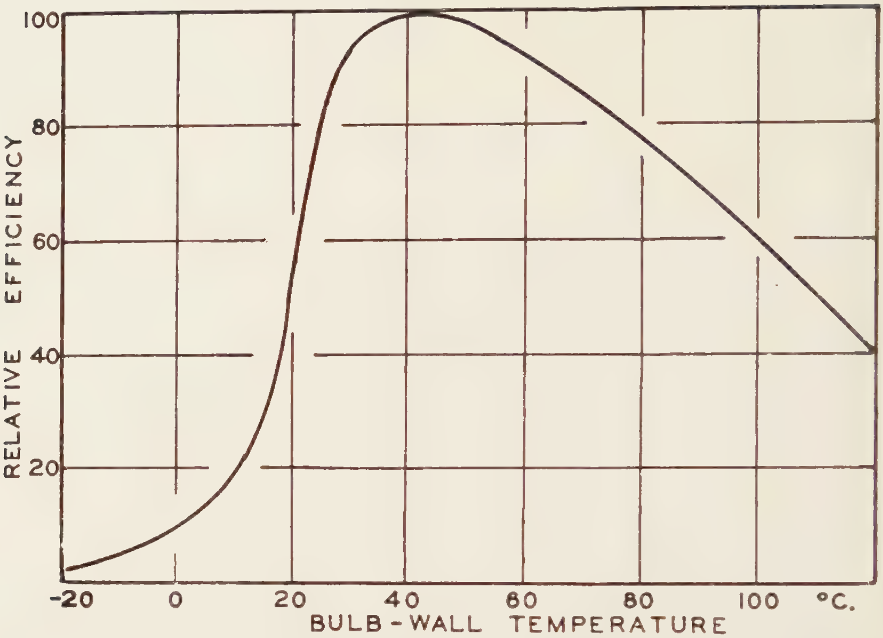


FIGURE 5. Efficiency of the generation of resonance radiation as a function of bulb-wall temperature.

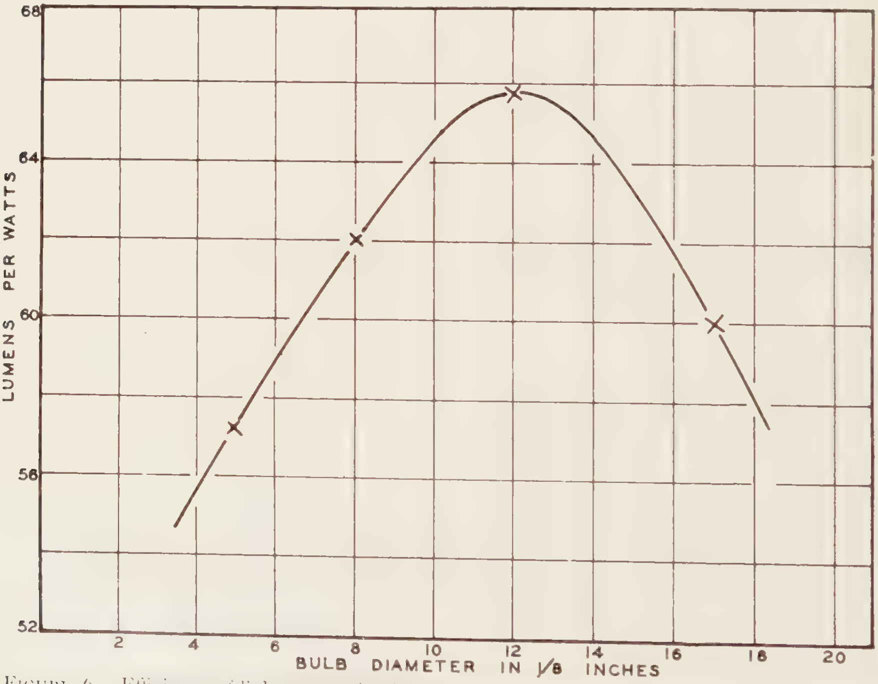


FIGURE 6. Efficiency of light generation in a fluorescent lamp as a function of bulb diameter.

mercury atom population increases, the resonance lines emitted near the axis of the discharge are strongly absorbed by the excited mercury atoms, with a resultant reradiation of other wave lengths. In other words, at high pressures (1 to 2 atmospheres) mercury arcs emit visible radiations at a high efficiency at the expense of resonance radiation. This phenomenon is sometimes called "imprisonment of radiation." In FIGURE 5 we see clearly the effect of bulb-wall temperature, and therefore mercury pressure, on the efficiency of the generation of resonance radiation. At low temperatures (below 40° C.), insufficient mercury atoms are available for excitation, and the generation of resonance radiation drops off very rapidly as the bulb-wall temperature is decreased. Conversely, at temperatures above 40° C. the imprisonment of radiation becomes more and more pronounced as the temperature rises until, at 100° C. and at a mercury pressure of 273μ, 2537 radiation falls off appreciably. At this temperature about 36 per cent of the input energy is emitted as resonance radiation, instead of 60 per cent under optimum conditions.

Bulb dimensions play an important part in the efficient generation of 2537 Å.[7] As might be expected, percentagewise, the longer the bulb the less the end losses, and therefore the higher the efficiency of the discharge tube as a radiation generator. It can also be shown very easily that bulb diameter is important. Not only does bulb diameter play an important role in the electrical parameters of the discharge but, as shown in FIGURE 6, there is an optimum bulb diameter from a radiation standpoint.[8] This curve was obtained by operating fluorescent lamps of various diameters at their maximum efficiency. The lengths of these lamps were so chosen that each had the same or nearly the same arc voltage. This arrangement eliminates the effect of end losses. It is obvious that there is a pronounced maximum at a bulb diameter of 12/8 in. The explanation of this is that at small diameters there is excessive energy loss due to recombination at the walls whereas with bulbs of large diameter the imprisonment of radiation becomes increasingly serious. These 2 phenomena are opposed to each other, with the result that there is a bulb diameter at which the combined effects of these processes become minimum and result in a maximum lamp efficiency.

Summary

An attempt has been made to show some of the more important uses of mercury in the field of electronics. The various physical properties of mercury that make it an element of unique importance in this field have been briefly discussed. The extreme importance of mercury, particularly in the vapor form, will be obvious to even the casual reader. If it were not for the peculiar physical properties with which mercury, and mercury alone, is endowed, we should not enjoy today the benefits of many extremely important electronic devices vital to modern civilization.

References

1. MARTI, O. K. & H. WINOGRAD. 1930. Mercury Arc Power Rectifiers. : 24. McGraw Hill. New York, N. Y.
2. LOEB, L. B. 1955. Fundamental Processes of Electrical Discharge in Gases. : 631-636 Univ. Calif. Press. Berkeley, Calif.

3. Langmuir, I. & H. Mott-Smith. 1924. Gen. Elec. Rev. **27:** 762.
4. Slepian, J. & L. R. Ludwig. 1933. Trans. Am. Inst. Elec. Engrs. **52:** 643.
5. Maxfield, F. A. & R. R. Benedict. 1941. Theory of Gaseous Conduction and Electronics. : 364. McGraw-Hill. New York, N. Y.

6a. Zwikker, C. 1952. Fluorescent lighting. : 63. Philips Tech. Libr. Eindhoven, Netherlands.

6b. Seeliger, R. 1927. Einführung in die Physik der Gas Entladungen. : 28. Barth. Leipzig, Germany.

6c. Uyterhoeven, W. 1938. Electrische Gasentladungslampen. : 53. Springer. Berlin, Germany.

7. Lowry, E. F. 1952. The Physical Basis for Some Aspects of Fluorescent Lamp Behavior. Illum. Eng. **47:** 639.
8. Lowry, E. F., W. C. Gungle & C. W. Jerome. 1954. Some Problems Involved in the Design of Fluorescent Lamps. Illum. Eng. **49:** 545.

RECENT STUDIES IN THE STRUCTURAL INORGANIC CHEMISTRY OF MERCURY

By William N. Lipscomb
University of Minnesota, Minneapolis, Minn.

Structural studies, chiefly by X-ray diffraction methods, during the last 10 years have helped to provide a basis for understanding chemical reactions of inorganic mercury compounds. The structural principles are much the same as those established in the older literature, but they have now elucidated the nature of some of the compounds known even to the alchemists. A brief review of the reactions of Hg(I) compounds with ammonia to yield Hg and certain Hg(II) compounds will be presented first; this will be followed by the few systematic groups of papers relating to mercuric oxide, to mixed oxides and chlorides and, finally, to thiocyanates of mercury. Discussion of organomercury compounds may be found in the chapter by G. F. Wright; hence they are not reviewed here. No attempt is made to achieve completeness in this review, but some attention is given to the more extended programs of research undertaken in this field during the past ten years.

Reactions Between Hg_2Cl_2 and Ammonia

The chemistry. Calomel and its reactions with ammonia to form a black precipitate were known to the ancient alchemists. This same reaction forms the basis for separation of Hg(I), Ag(I), and Pb(II) in the usual qualitative analysis schemes. These ions are precipitated as their chlorides, the $PbCl_2$ is leached out with hot water, and then ammonia is added to dissolve AgCl as $Ag(NH_3)_2^+$, leaving a gray or black precipitate. Most textbooks call this precipitate Hg + $HgNH_2Cl$ and, under certain conditions of concentrations of reagents and products, this is correct. Under other conditions, however, other products are formed. The existing literature before 1951 is so varied and confusing on this problem that it is not reviewed here, but among a very long list of products[1, 2] Hg_2O, $Hg_4NCl(H_2O)$, Hg_2NH_2Cl, $Hg_2(NH_3)_2Cl_2$, $Hg_2NCl(H_2O)$, $HgNH_2Cl$, and $Hg(NH_3)_2Cl_2$ appear in the most recent works before 1951. Although these earlier investigators used physical methods, such as X-ray diffraction, for the first time on this problem, they did not complete structure determinations of these materials, and their diffraction patterns were not always of pure materials.

A chemical investigation guided by X-ray powder-diffraction patterns has now led to the establishment of the conditions under which pure materials are produced and, subsequently, to the structures of these materials. In the first place, the presence of Hg_2O, or the hydroxide, and the presence of $Hg_4NCl(H_2O)$, Hg_2NH_2Cl or $Hg_2(NH_3)_2Cl_2$ were all disproved as compounds or intermediates that would yield crystalline diffraction patterns.[3, 4] For example, the identification of the diffraction patterns of Egidius, or Gleditsch and Egidius, is as follows: the diffraction pattern of Hg_2NH_2Cl is actually cubic $Hg_2NCl \cdot H_2O$; that of $Hg_2(NH_3)_2Cl_2$ is a mixture of $Hg(NH_3)_2Cl_2$ and

Hg_2Cl_2 ; that for Hg_2NH_2Cl is $HgNH_2Cl$ (and different from the pattern in an earlier paper of the series); that for $Hg_4NCl(H_2O)_x$ is cubic $Hg_2NCl \cdot H_2O$; and that given for the authentic sample of $Hg_2NCl \cdot H_2O$ prepared by another method is the hexagonal form of $Hg_2NCl \cdot H_2O$.

The reactions of Hg_2Cl_2 with ammonia (aqueous), as traced by a combination of chemical and X-ray diffraction techniques, are actually not complicated. Hg(I) is converted to Hg and Hg(II), and we observe powder patterns of only 3 Hg(II) compounds: $Hg_2NCl \cdot H_2O$, $HgNH_2Cl$, $Hg(NH_3)_2Cl_2$. Which of these is formed depends upon the concentration of NH_4Cl, which is produced in the reactions.

$$2Hg_2Cl_2 + 4NH_3 + H_2O = 2Hg + Hg_2NCl \cdot H_2O + 3NH_4Cl$$

$$Hg_2Cl_2 + 2NH_3 = Hg + HgNH_2Cl + NH_4Cl$$

$$Hg_2Cl_2 + 2NH_3 = Hg + Hg(NH_3)_2Cl_2$$

These are the over-all reactions, and it is easy to convert from $Hg_2NCl \cdot H_2O$ to $HgNH_2Cl$ to $Hg(NH_3)_2Cl_2$ by adding NH_4Cl, or simply by failing to remove it from the solution. Conversely, if NH_4Cl is removed or if the ammonia is sufficiently dilute the interconversions go in the reverse direction, toward $Hg_2NCl \cdot H_2O$.

The crystal chemistry. Because all of the compounds produced from Hg_2Cl_2

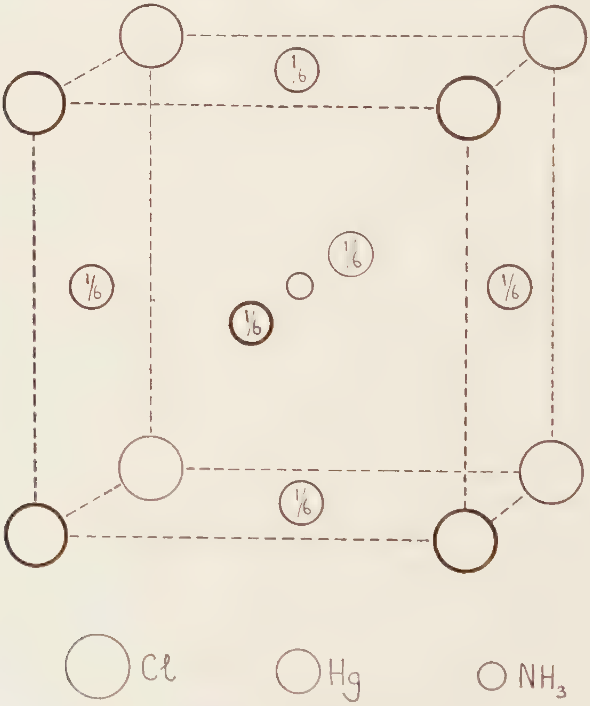


FIGURE 1. Statistical structure of $Hg(NH_3)_2Cl_2$.

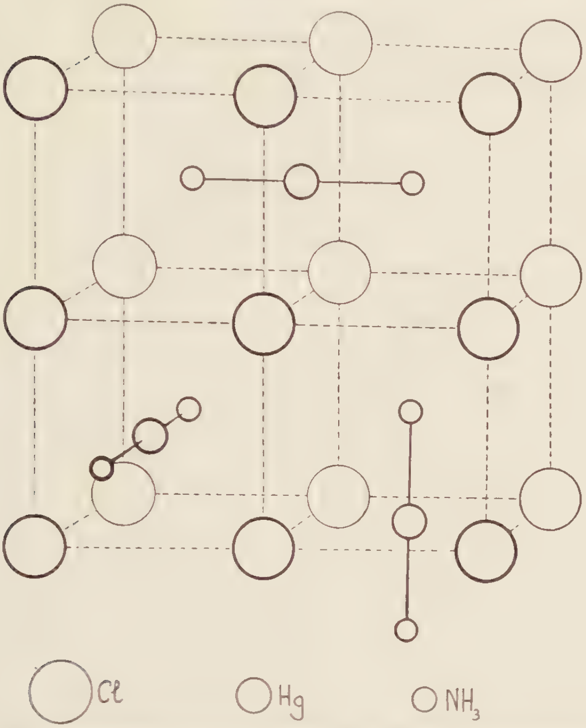


FIGURE 2. Reinterpretation of the structure of $Hg(NH_3)_2Cl_2$, showing the statistical disorder of linear $^+H_3N—Hg—NH_3^+$ ions.

are really Hg(II) compounds, it makes no difference if one starts with Hg(I) or Hg(II). The detailed structures of $Hg(NH_3)_2Cl_2$, $HgNH_2Cl$, $Hg_2NCl \cdot H_2O$ are very closely related, and they furnish convincing proof that these are really Hg(II) compounds and not double salts: for example, $HgNH_2Cl$ is not $Hg_2NCl \cdot NH_4Cl$, as has been suggested in the early literature.

The structure of $Hg(NH_3)_2Cl_2$ was elucidated by MacGillavry and Bijvoet,[5] who derived the statistical structure shown in FIGURE 1 and reinterpreted this result on the sound chemical grounds shown in FIGURE 2. The characteristic ions are linear $^+H_3N—Hg—NH_3^+$ (except for hydrogen) and Cl^-. The statistical disorder is obtained by orienting these linear ions along the crystallographic *a*, *b*, or *c* axes of the cubic unit cell at random.

The orthorhombic structure[6] of $HgNH_2Cl$ (FIGURE 3) consists of infinite chains $—Hg—NH_2—Hg—NH_2—$, in which the bonds about Hg are linear and those about N are tetrahedral. Hydrogen atoms were not located in any of the X-ray studies, and hence the assumption of tetrahedral hybrids (sp^3) about N is only an inference from the stoichiometry and the usual structural analogies. It is important, therefore, that a study[7] of the nuclear magnetic resonance of solid $HgNH_2Cl$ has established the tetrahedral character of bonds about N, and is consistent with the X-ray results. Spectroscopic studies are

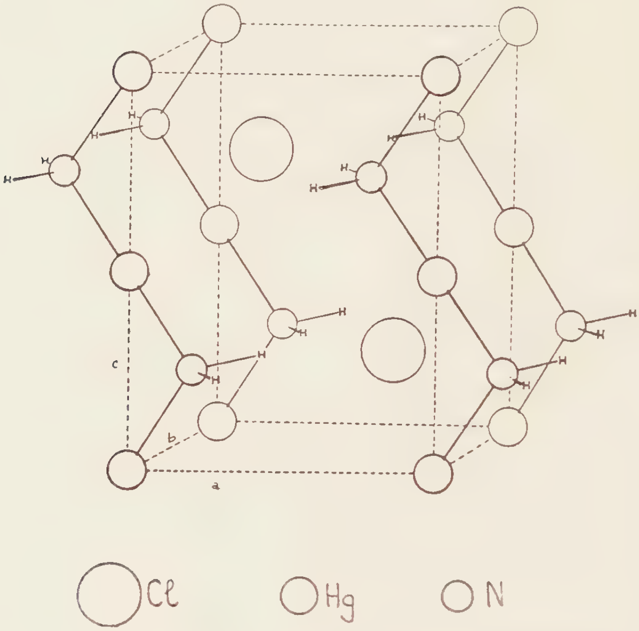


FIGURE 3. Structure type of $HgNH_2Cl$ and $HgNH_2Br$.

now under way elsewhere, and the results are awaited with interest. An independent,[8] but as yet unpublished, X-ray diffraction study of single crystals also confirms this structure of $HgNH_2Cl$.

$Hg_2NCl \cdot H_2O$ is the chloride of Millon's base,[9] $Hg_2NOH \cdot 2H_2O$. It exists in several modifications that are based either on the cubic cristobalite (SiO_2) or the hexagonal tridymite (SiO_2) arrangements or on slight distortions of these 2 structures. The linear —Hg— groups replace the not-so-linear —O— groups and the tetrahedral N atoms replace the tetrahedral Si atoms in the SiO_2 structures. The cubic form is shown in FIGURE 4. Large channels remain in this structure, and the negative ions and water molecules that occupy these channels are easily exchanged. In all of these exchange reactions the 3-dimensional Hg_2N^+ framework, which is strongly bound, remains constant.

Thus in all of these compounds the linear bonds about Hg, the tetrahedral bonds about N and the analogies with SiO_2 structures are observed. Finite groups occur in $^+H_3NHgNH_3{}^+$ ion, chains in $HgNH_2Cl$, and 3-dimensional networks in Hg_2N^+ compounds. We shall ask whether sheets can occur to complete the analogy, and shall see that they do in Hg_2NHBr_2 as has recently been demonstrated by Brodersen.[10] Possibly a quartz-like arrangement for Hg_2N^+ will also be found, but perhaps too much distortion is required.

Mineralogy. It is most remarkable that some of these compounds can occur as minerals, but mosesite[11] has the cubic $Hg_2NCl \cdot H_2O$ structure, and kleinite has a hexagonal structure that may be related to hexagonal $Hg_2NCl \cdot H_2O$. Probably both of these compounds are formed in nature by reactions similar to

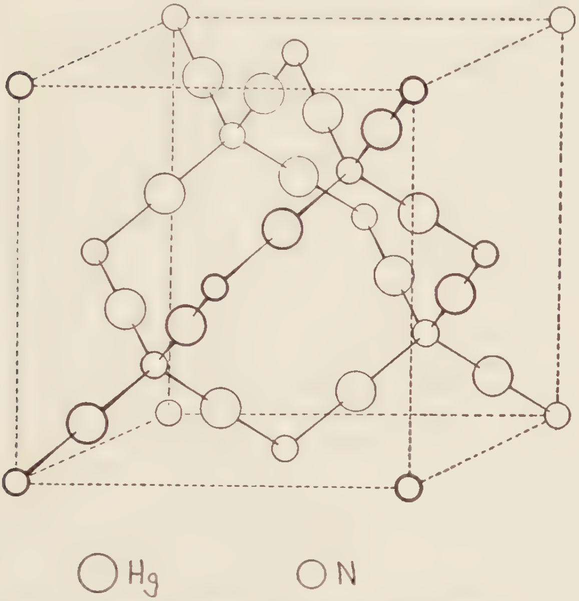


FIGURE 4. Hg_2N^+ framework of Millon's base, $Hg_2NOH \cdot 2H_2O$.

those described above. For example, calomel, mosesite, and native Hg are associated,[11] and sometimes organic matter that could be the source of ammonia is associated.

The identity of mosesite and cubic $Hg_2NCl \cdot H_2O$ is clearly established, but some remarks on the structure of kleinite are appropriate. Hexagonal tridymite-like Hg_2NBr has cell dimensions[12, 13] of $a = 6.65$ and $c = 11.26$ A, while Heritsch's later work[14] indicates that for kleinite $a = 13.56$ and $c = 11.13$. In our unpublished studies[11] we have taken a number of single crystal diffraction patterns that indicate at least 16 faint reflections that cannot be indexed on the unit cell given by Heritsch, and that seem to require that the value of a as given by him should be tripled. These reflections are faint, and can probably be ignored in the first approximations to the structure, but it is unsafe to ignore the moderately intense reflections that cause the value of $a = 13.56$ A to be double that of 6.65 A for hexagonal Hg_2NBr. Moreover, the powder-diffraction pattern of kleinite is sufficiently different from that of hexagonal Hg_2NBr to cause us to remark[13] that there are major differences in these structures. Preliminary calculations of intensities of the hk0 reflections of single crystals suggest that some additional Hg atoms are present in the channels of the tridymite-like structure and that, in addition, significant changes occur in the positions of the Hg atoms from their idealized positions in the tridymite-like structure. These results are also in agreement with the chemical analyses, and possibly the structure of kleinite will eventually become established as a distorted tridymite-like Hg_2NBr with additional Hg(II) in the channels. Indeed, these impurities may stabilize the structure. Finally, a further careful investigation is needed to establish the relation between kleinite, which contains combined nitrogen, and $Hg_4O_3Cl_2$, which does not. K. Aurivillius[20a, b] has remarked that these two substances are apparently identical.

Reactions of Hg_2Br_2 with Ammonia

The compounds produced when Hg_2Br_2 is used as a starting material are always Hg(II) compounds, but the reactions are somewhat more complicated than those for Hg_2Cl_2, and at least 2 new compounds are observed. Most of the studies of these compounds have been done in Tübingen, Germany, by Brodersen and Rüdorff. In summary, the series of compounds is

Hg_2NBr (hexagonal)[12, 13]
Hg_2NHBr_2 (hexagonal)[15a]
$HgNH_2Br$ (orthorhombic)[16, 17]
$HgNH_2Br$ (cubic)[16]
$Hg(NH_3)_2Br_2$ (cubic)

These investigators have established with care the conditions under which these compounds are formed. They have shown[18] that the hexagonal form of Hg_2NBr is more stable than the cubic form; that the formation of orthorhombic $HgNH_2Br$ requires[17] the presence of slight impurities of $HgBr_2$; that cubic $Hg(NH_3)_2Br_2$ and cubic $HgNH_2Br$ form[19] a series of solid solutions; and a host of other chemically interesting results.

An important contribution to the crystal chemistry of these compounds is Brodersen's[15b] discovery of the sheetlike structure of Hg_2NHBr_2. This hexagonal arrangement of $(Hg_2NH^{++})_\infty$ (FIGURE 5) completes the analogy with the

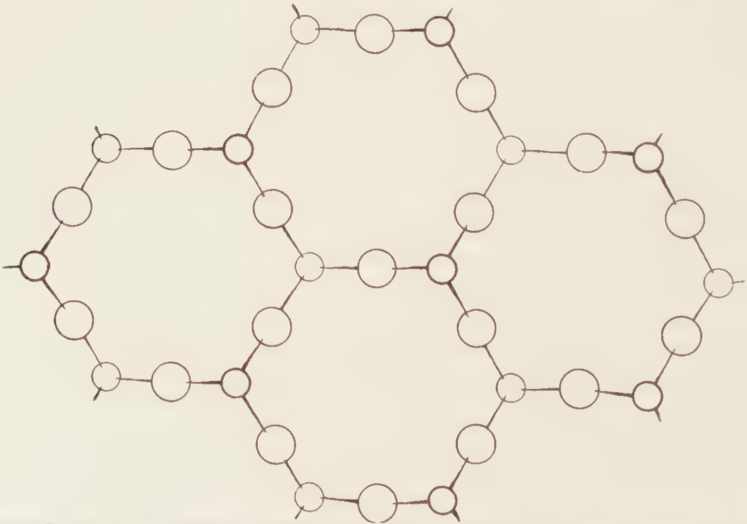


FIGURE 5. Puckered $[(NH)_2Hg_3^{+2}]_\infty$ layer in Hg_2NHBr_2. There are also Br^- in the holes of these layers, and triangular $HgBr_3^-$ groups between these layers. Small circles are NH pointed up (heavy circle) or down (light circle). The larger circles are Hg atoms.

silicates and, like all of the other structures, Hg forms linear bonds, while N forms tetrahedral bonds.

There remain a number of interesting problems, not the least of which is a thorough study of the iodide series. This series is somewhat complicated by the tendency to the formation of soluble complexes with Hg(II). A spectroscopic study of solid solutions of $HgNH_2Br$ in $Hg(NH_3)_2Br_2$ may also indicate how the long chains of $HgNH_2Br$ fit into the $Hg(NH_3)_2Br_2$ structure, since comparison of the dimensions of the chains and the unit cell dimensions suggest some distortion.

Hg(II) Oxide and Oxychlorides

The structure of HgO is very much like that of $HgNH_2^+$ in $HgNH_2Cl$. Infinite zigzag chains of ···HgO HgO HgO··· exist with linear bonds about Hg and a bond angle HgO Hg of 109°. This conclusion of K. Aurivillius[20a, b] from a single crystal study is both more reliable and more reasonable on chemical grounds than the results obtained recently by Roth[20c] from a powdered sample.

The mercuric oxychlorides of the general formula $mHgCl_2 \cdot nHgO$ have been analyzed by X-ray diffraction methods. $HgCl_2 \cdot 2HgO$ is best represented[21] as $Hg(OHgCl)_2$ with Hg^{++} and polymeric anions $(OHgCl)^-$. Each Hg of the polymeric $(OHgCl)^-$ is surrounded by a distorted tetrahedron of 3 oxygen atoms and 1 chloride atom, and these tetrahedra are linked in layers so that each Cl belongs to only 1 Hg (2.66 A), and each O belongs to 3 Hg (2.16 A). The Hg^{++} is surrounded by a distorted octahedron of 2 oxygen atoms (at 2.49 A) and 4 chlorine atoms (at 2.94 A).

Several studies, summarized by Scavnicar and Grdenic,[22] have been published on $2\ HgCl_2 \cdot HgO$, which consists of $(ClHg)_3O^+$ cations and Cl^- anions. The Cl—Hg—O atoms are linear, and the ion $(ClHg)_3O^+$ is planar and has trigonal symmetry (FIGURE 6). Distances are Hg — O = 2.03 A and HgCl = 2.28 A in the cation. The $Hg \cdots Cl^-$ distances are 2.94 and 23.13 A. The planar configuration about the oxonium oxygen is remarkable, and it may suggest that the lone pair in the P_z-type orbital normal to the plane of sp^3 hybridization participates in bonding to the unused P_z orbitals of the Hg atoms.

A more precise value of 2.25 A has been determined[23] by Grdenic for the HgCl distance in $HgCl_2$. This value is in good agreement with earlier values; it is in fair agreement with the value[24] of 2.34 A in $NH_4Cl \cdot HgCl_2$ and in poor agreement with the value of 2.50 found[25] in the disordered mercury alkyl chlorides, CH_3HgCl and PrHgCl.

Hg(II) Thiocyanates

A series of studies of thiocyanates of various metals by Zhdanov, Zvonkova, and Sanadze[27a-k] has yielded some interesting comparisons of Hg with other metals. In Br—Hg—SCN the bonding about Hg is approximately linear, but the SCN group is not along this same line. In $KHg(SCN)_3$ there are K^+, SCN^-, and $Hg(SCN)_2$ groups, and the S—Hg—S angle is about 155°, having been distorted apparently by the more distant largely ionic SCN^-. In

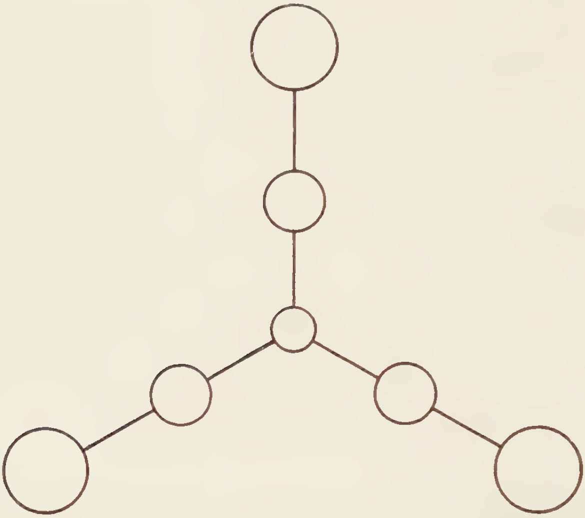


FIGURE 6. The $(ClHg)_3O^+$ cation in $2HgCl_2 \cdot HgO$. The largest circles are Cl, and the smallest circle is O. The ion is planar and has the indicated threefold symmetry.

$K_2Hg(SCN)_4$ the Hg is bonded at covalent distances to the S atoms of the SCN group, but in $K_2Co(NCS)_4 \cdot 4H_2O$ the Co is bonded tetrahedrally to the N atoms; the corresponding Zn^{II} compound is like this Co^{II} compound. These results, and others in this series of papers, clarify a large body of information about the thiocyanates themselves.

A reasonably complete summary of earlier values of bond distances and a discussion of coordination about Hg has been given by Wells.[26] While both Hg(I) and Hg(II) tend to form linear bonds in most of their compounds, higher coordination occurs, such as tetrahedral coordination in red HgI_2, six (octahedral) coordination in $CsHgCl_3$, and eight (cubic) coordination in the highly ionic HgF_2, which has the fluorite structure. Any extrapolation, therefore, of the coordinations in the solids to those of ions in solution must be made with considerable caution.

References

1. Freche, H. & M. C. Sneed. 1938. J. Am. Chem. Soc. **60:** 518.
2. Gleditsch, E. & T. F. Egidius. 1936. Compt. rend. **202:** 574; Z. anorg. Chem. **226:** 265; **228:** 249. T. F. Egidius. 1938. Z. anorg. Chem. **240:** 97. References to the older literature are given in these papers.
3. Arora, S. D., W. N. Lipscomb & M. C. Sneed. 1951. J. Am. Chem. Soc. **73:** 1015.
4. Nijssen, L. & W. N. Lipscomb. 1952. J. Am. Chem. Soc. **74:** 2113.
5. MacGillavry, C. H. & J. M. Bijvoet. 1936. Z. Krist. **94:** 231.
6. Lipscomb, W. N. 1951. Acta Cryst. **4:** 266.
7. Deeley, C. M. & R. E. Richards. 1954. J. Chem. Soc. **:** 3697.
8. Lingafelter, E. C. 1951. Private communication.
9. Lipscomb, W. N. 1951. Acta Cryst. **4:** 156.
10. Brodersen, K. 1955. Acta Cryst. **8:** 723.
11. Switzer, G., W. F. Foshag, K. J. Murata & J. J. Fahey. 1953. Am. Mineralogist. **38:** 1225.
12. Rüdorff, W. & K. Brodersen. 1952. Angew. Chem. **64:** 617.
13. Nijssen, L. & W. N. Lipscomb. 1954. Acta Cryst. **7:** 103.

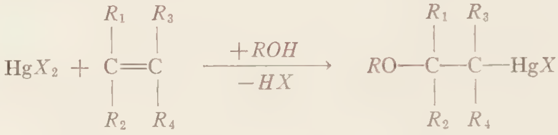
14a. Moore, E. B., Jr. & W. N. Lipscomb. To remain unpublished.
14b. Heritsch, H. 1949. Tschermaks mineralog. u. petrog. Mitt. **1:** 300.
14c. Heritsch, H. 1954. Österr. Akad. Wiss. Sitzber. : 1.
15a. Brodersen, K. & W. Rüdorff. 1954. Z. Naturforsch. **9***b*: 164.
15b. Brodersen, K. 1955. Acta Cryst. **8:** 723.
16. Nijssen, L. & W. N. Lipscomb. 1952. Acta Cryst. **5:** 604.
17. Brodersen, K. & W. Rüdorff. 1954. Z. anorg. u. allgem. Chem. **275:** 141.
18. Rüdorff, W. & K. Brodersen. 1953. Z. anorg. u. allgem. Chem. **274:** 323.
19. Rüdorff, W. & K. Brodersen. 1952. Z. anorg. u. allgem. Chem. **270:** 145.
20a. Aurivillius, K. 1954. Acta Chem. Scand. **8:** 523.
20b. Aurivillius, K. 1956. Acta Cryst. **9:** 685.
20c. Roth, W. L. 1956. Acta Cryst. **9:** 277.
21. Scavnicar, S. 1955. Acta Cryst. **8:** 379.
22. Scavnicar, S. & D. Grdenic. 1955. Acta Cryst. **8:** 275.
23. Grdenic, D. 1950. Arhiv Kem. **22:** 14.
24. Harmsen, E. J. 1938. Z. Krist. **100:** 208.
25. Grdenic, D. & A. I. Kitaigorodskii. 1949. Zhur. Fiz. Khim. **23:** 1161.
26. Wells, A. F. 1950. Structural Inorganic Chemistry. 2nd ed. : 631–634. Clarendon Press. Oxford, England.
27a. Zhdanov, G. S. & V. V. Sanadze. 1952. $Hg(SCN)_2$-ASCN where A = K or NH_4. Zhur. Fiz. Khim. **26:** 469.
27b. Zvonkova, Z. V. & G. S. Zhdanov. 1952. Paper V, HgClSCN. Zhur. Fiz. Khim. **26:** 586.
27c. Zhdanov, G. S. & Z. V. Zvonkova. 1951. $K_2Co(NCS)_4$. Izvest. Sektora Platiny i Drug. Blagorod. Metal. Inst. Obshcheĭ i Neorg. Khim. Akad. Nauk S.S.S.R. **26:** 235.
27d. Zvonkova, Z. V. 1953. $K_3Rh(SCN)_6$. Zhur. Fiz. Khim. **27:** 100.
27e. Zhdanov, G. S., Z. V. Zvonkova & V. P. Glushkova. 1953. $K_3Cr(SCN)_6$, $4H_2O$, $K_4Ni(SCN)_6$, $4H_2O$, $PbPt(SCN)_6$. Zhur. Fiz. Khim. **27:** 106.
27f. Zvonkova, Z. V. 1952. $K_2Zn(NCS)_4$, $K_2Cd(SCN)_4$, $K_2Hg(SCN)_4$. Zhur. Fiz. Khim. **26:** 1798.
27g. Zvonkova, Z. V. 1952. $K_2Pt(SCN)_4$. Zhur. Fiz. Khim. **26:** 1804.
27h. Zhdanov, G. S. & Z. V. Zvonkova. 1954. $K_2Cd(SCN)_4 \cdot 2H_2O$. Trudy Inst. Krist. Akad. Nauk S.S.S.R. **9:** 221.
27i. Zhdanov, G. S. & Z. V. Zvonkova. 1952. Zhur. Fiz. Khim. **26:** 586.
27j. Zhdanov, G. S. & Z. V. Zvonkova. 1953. Uspekhi Khim. **22:** 3.
27k. Zhdanov, G. S. & Z. V. Zvonkova. 1953. Doklady Mezhdunarod. Kongr. Teoret. i Priklad. Khim. XIII Kongr. **135.** Stockholm, Sweden. (Cf. also **175** for a French translation.)

OXYMERCURATION OF ALKENES

By George F Wright

Department of Chemistry, University of Toronto, Toronto, Ont., Canada

In 1901, Julius Sand[1] found that alkenes would react with an aqueous solution of mercuric nitrate. Further work in the laboratories of Sand, of W. Schrauth, and of Biilmann[7a, 7b] showed that the reaction was one in which basic mercuric salts were added to the double bond, as shown in EQUATION 1. The salt was usually mercuric acetate or basic mercuric nitrate, and the alcoholic group (ROH) was either water, a primary alcohol or, sometimes, a part of one of the substituent groups, R_1, R_2, R_3, and R_4. In the latter case the product was a cyclic ether that formed even when a large amount of hydroxylic solvent was present.



$$\text{Hg}X_2 + R_1R_2\text{C}{=}\text{C}R_3R_4 \xrightarrow[-HX]{+ROH} R\text{O}{-}\text{C}R_1R_2{-}\text{C}R_3R_4{-}\text{Hg}X$$

(I) (II)

The addition compounds were often found to be unstable in the presence of acids, especially aqueous hydrogen halides, that decomposed the oxymercurial to regenerate the alkene by a reversal of the equation shown above. In some cases this reversibility was effected by the acid formed in the reaction, so that low yields of product were obtained even when mercuric acetate was used as the salt. In fact, this easy reversibility led Manchot[2] to the opinion that the structure for the oxymercurial that is shown above was less in conformity with experimental fact than that of a molecular complex, which he expressed as $R_1R_2\text{C} = \text{C}R_3R_4 \cdot R\text{OHg}X$.

This opinion that the oxymercurials were loose molecular complexes, such as those formed by alkenes with cuprous, silver, and platinum salts, was derived from the apparent instability of these compounds. This undoubtedly discouraged use of the reaction by those investigators who wished to study the mechanism involved in the saturation of a double bond. This was perhaps unfortunate, because the reaction has certain features, to be outlined later in this paper, that are more definitive than those of additions such as bromination, hydroxy-bromination, hydrogenation, and the like.

Chemists at the University of Illinois, Urbana, Ill., were instrumental in proving the fallacy of Manchot's[2] hypothesis respecting the structure of the oxymercurials. By adding mercuric acetate to *o*-allylphenol, Adams and his co-workers,[3] produced 2-acetoxymercurimethylbenzofuran. This demonstration of double-bond saturation was followed by Marvel's[4] methoxymercuration of optically active cinnamic esters. Marvel's proof that 2 new asymmetric centers were produced by addition of the elements of methoxymercuric acetate disposed of Manchot's hypothesis in favor of the bond-saturation hypothesis originally proposed by Sand.[1]

Actually, the stability of oxymercurials with respect to acidic reagents varies widely with respect to the alkene which is involved. Sand[1] showed that ethylene could be oxymercurated by basic mercuric sulfate in water at *p*H 2. An 83 per cent yield in 1-molar nitric acid or 63 per cent in 2-molar nitric acid of 2-hydroxycyclohexylmercuric chloride is obtained when cyclohexene is treated with mercuric nitrate, and the system then is treated with 1 equivalent of sodium chloride. The yield is insignificant, however, when more than 1 equivalent of sodium chloride is present, thus demonstrating the effectiveness of hydrogen halide[5] as a demercurating agent for the oxymercurials. On the other hand, 1,4-$\wedge\wedge$-methylene-5-cyclohexene-2,3-$\downarrow\downarrow$-dicarboxylic acid may be oxymercurated by an aqueous solution of mercuric chloride, and the 95 per cent yield thus obtained is decreased to only 80 per cent by inclusion of an extra equivalent of hydrochloric acid.

As might be expected, addition to the double bond occurs, so that the oxy group attaches itself to the more electropositive carbon and the mercury to the more electronegative carbon of the double bond. For this reason, mercury appears at the ultimate carbon atom of a terminal double bond. Furthermore, unless the polarities of these carbon atoms are almost identical,[6] the addend seems to be capable of close discrimination, so that only 1 positional isomer is usually encountered.

A further characteristic of this specificity of addition was discovered by Biilmann,[7] who could oxymercurate *cis* but not *trans* cinnamic acid, and maleic but not fumaric acid. It was shown later[8] that this discrimination was one of rate, where *cis* isomers always oxymercurate faster than the *trans* forms. Furthermore, each of the geometric isomers yields its characteristic diastereoisomer uncontaminated with the other. Thus, referring to the previously mentioned equation, if R_1 and R_3 are phenyl (R_2 and R_4 are hydrogen), the reaction of each of the geometric isomers of stilbene will yield, from a solution of methanol, a different 1-methoxy-2-acetoxymercuri-1,2-diphenylethane.

These diastereoisomers are not ordinarily interconvertible. Thus the acidic group on the mercury atom (X in the above formulation, which may be acetate or nitrate in the original product) seems to be capable of ionization, since it can be exchanged in aqueous solution with hydroxide, to give a water soluble base, or with chloride. The chloromercuri compound can be converted almost completely to the bromomercuri derivative by treatment with 1 equivalent of aqueous sodium bromide, and the latter derivative is converted to the iodomercuric compound by treatment with sodium iodide. This alkylmercuric iodide tends to be unstable, like the analogous thiocyanate[2] and cyanide,[1] and regenerates the alkene, though the benzoate is quite stable.[8] All of these highly crystalline derivatives are related configurationally to the original reaction product from 1 geoisomeric alkene.

The oxymercurials, and especially the methoxymercurials, are thus good derivatives for identification of *cis-trans* isomers and, during their preparation, the choice can be made as to which is the *cis* form, since the rate of reaction of this form will be faster than that of the *trans* isomer. This rate of reaction may be followed by analysis for mercury that has not reacted, after chloroform extraction to remove the methoxymercurial, by means of titration with thiocyanate at high concentration or with dithizon when the dilution is high. When a catalyst is rigorously excluded, the reaction appears to be bimolecular, at least during the early stages, and the linear reciprocal concentration plot against time has been used to evaluate the composition of geoisomeric mixtures.[9]

Thus the oxymercuration reaction is useful for characterization of positional or geometric isomers of alkenes, but attention must also be given to catalysis. The reaction is inhibited by the presence of electron donors such as pyridine or various nitriles, probably owing to the tendency of such substances to coordinate with mercuric salts. Although the addition reaction is not sensitive to small amounts of these inhibitors, it is accelerated strongly by small amounts of boron fluoride or peroxides. The function of the boron fluoride, an electron acceptor, is understandable, but no adequate explanation of the action of peroxides has yet been devised. It may be significant that the addition of hydrogen peroxide to methanolic mercuric acetate causes a yellow coloration; when this bleaching occurs mercurous acetate is precipitated and the catalyst disappears. It should be noted that peroxides and boron fluoride are not supplementary but, rather, complementary and specific for certain alkenes in the addition reaction; the mechanism of catalysis for each may not be the same. Nevertheless, the catalytic effect of added boron fluoride also decreases in respect of time. In practice, it is advisable to exclude both types of catalyst if one wishes to maintain constancy of the rate of oxymercuration unless the catalyst is supplied continually to the reaction.[10]

The easy interchangeability of anion in the 2-oxyalkylmercuric salts provides a wide range of alkene derivatives suitable for identification, but the stereochemical structure of the salts has not been disclosed by their chemical reactions. The anionomercury group can often be removed by alkaline reducing agents[7, 8, 11] to yield the oxyalkane, but the configuration is thus lost. The same group may sometimes be replaced by bromine[1] or iodine.[2] The original configuration is lost, however, as indeed may be expected whenever replacement occurs at a carbon-metal linkage.

It should not be inferred that these reduction and halogenation reactions are entirely general in application. In many cases such treatment only serves to eliminate the addend, oxymercuric salt, and thus regenerate the alkene. Indeed, this regeneration is the only *general* reaction of the 1-oxy-2-alkylmercuric salts. It does not always occur, but it may be anticipated. Thus it has been found that diaryltin dihalides react to give an unsymmetrical diarylmercury,[12]

$$2\ \mathrm{HOC_2H_4HgCl} + \mathrm{Ar_2SnCl_2} \rightarrow 2\ \mathrm{HOC_2H_4HgAr} + \mathrm{SnCl_4} \qquad (2)$$

but other organometallic compounds, such as Grignard reagents, serve to regenerate an equilibrium mixture of *cis* and *trans* alkene,[8]

$$\mathrm{C_6H_5{-}CH(OCH_3){-}CH(HgCl)C_6H_5} + \mathrm{RMg}X \rightarrow$$

$$\mathrm{C_6H_5CH = HC{-}C_6H_5} + \mathrm{RHgCl} + \mathrm{CH_3OMg}X \qquad (3)$$

Likewise, the regeneration of alkene occurs on treatment with diazomethane,[13] alkyl halides,[2, 14] and acyl halides in acidic media.[8] In alkaline or neutral media the hydroxyl group in 2-hydroxyalkylmercuric salts can sometimes be acylated[11, 14] or caused to react with phenylisothiocyanate,[12] but these reactions do not contribute to proof of stereochemical structure.

Suggestions for the mechanism of oxymercuration were based at first on the idea that mercuric salt added to the double bond as acyl and acylmercuric groups, after which the acyl group suffered exchange with a hydroxy or alkoxy group. Although addition products of mercuric acetate with alkenes are known,[15] there are several objections to such a mechanism. First, a typical addition compound of this type, 1-acetoxy-2-acetoxymercuricyclohexane, has been found to react much more slowly with methanol than does a mixture of mercuric acetate and cyclohexene in the same medium.[16] This means that, according to the mechanism outlined above, the rate-controlling step in excess of methanol would follow first-order kinetics. Actually, the observed kinetic behavior is of the second order. Furthermore, the behavior of 1-acetoxy-2-acetoxymercuricyclohexane in aqueous solution indicates that it reacts by dissociating first into cyclohexene and mercuric acetate, since the latter substance can be detected in the reaction mixture.

An alternative mechanism would involve the prior rapid reaction of mercuric acetate (III) with the hydroxylic solvent.

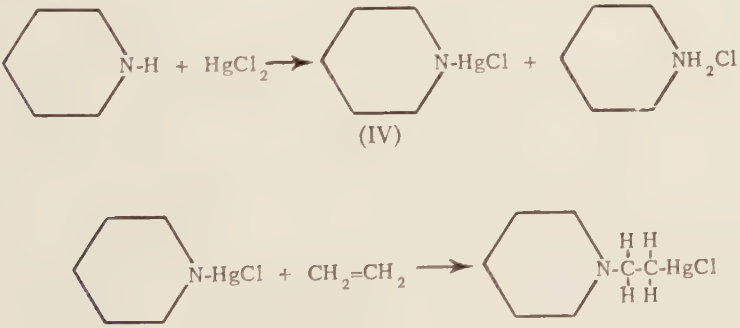
$$\mathrm{Hg(OAc)_2 + CH_3OH \rightleftarrows \underset{(III)}{CH_3O{-}HgOAc} + HOAc} \tag{4}$$

The methoxymercuric acetate, which then presumably adds to the double bond, never has been isolated. Its existence has been justified, however, as a reasonable explanation for the second-order kinetics that are observed during the oxymercuration of cyclohexene.

Further justification for the existence of methoxymercuric acetate as a reactive species is afforded by a recent variation of the oxymercuration reaction wherein piperidine, a secondary amine, replaces alcohol.[17] Amines ordinarily react with mercuric salts according to the equation shown below.

$$\mathrm{(X)\ NH_3 + HgCl_2 \rightarrow H_2N{-}HgCl + NH_4Cl} \tag{5}$$

Analogously, piperidine would be expected to react accordingly to yield IV in FIGURE 1.



(IV)

(V)

FIGURE 1

The 65 per cent yield of 2-piperidylethylmercuric chloride (V), which the Russian workers obtained by treatment of ethylene with piperidine and mercuric chloride, may be formulated as shown.

Since the structure of the product was proved by sodium-amalgam reduction to be *N*-ethylpiperidine (and it does not precipitate mercuric oxide with alkali, yet evolves ethylene when treated with potassium cyanide), it seems to be analogous with the oxymercurials.

Assuming, then, that the addend in oxymercuration is basic mercuric salt, the mode of its addition comes into question. The simplest hypothesis would involve, for methoxymercuration, the addition of methoxy and acetoxymercuri fragments, either as free radicals or as ions. Although the peroxide catalysis might suggest a free-radical mechanism, the production of a single diastereomer from one geoisomeric alkene renders such a concept improbable.

A simple ionic hypothesis is even less probable. First, the ionic concentration should depend on the polarity of the solvent. In this event, hydroxymercuration should be more rapid than methoxymercuration, but the converse is true.[16] Actually, ionic transport for mercuric acetate in methanol is negligible, although it is appreciable in water. In consequence, it is believed that the basic mercuric salt adds molecularly to the alkene. An example (FIGURE 2) is afforded by the treatment of 2,6-dimethyl-5-heptene-2-ol (VI) with "neat" mercuric acetate (X = OAc) or alternatively with aqueous mercuric acetate.[15] Although mercuric acetate is not soluble as such, in dimethylheptenol, an equivalent of the salt disappears into 4 equivalents of the alcohol within an hour

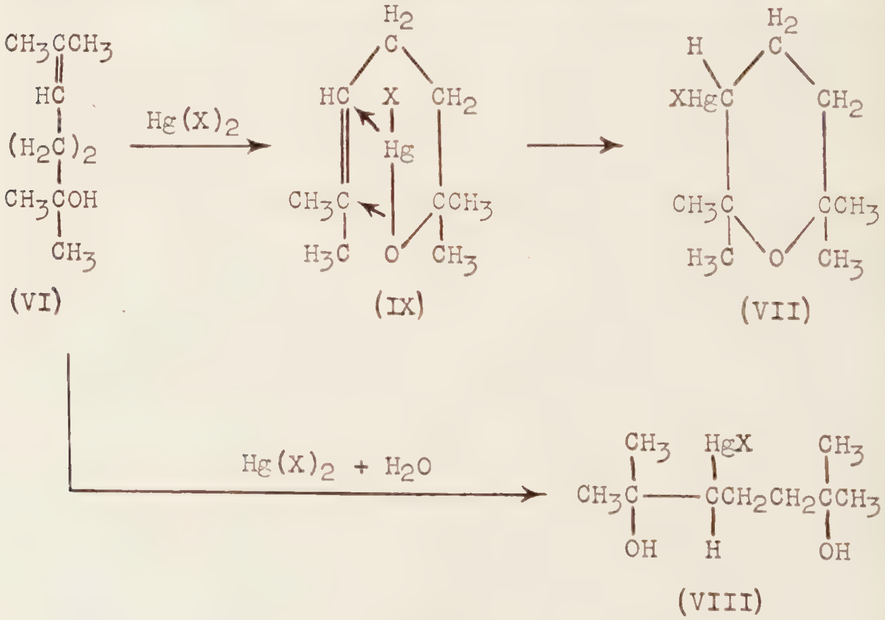


FIGURE 2*

* Reproduced by permission of the *Journal of Applied Chemistry*.

at 25–30° C. A 91 per cent yield of 2,2,6,6-tetramethyl-3-chloromercuri tetrahydropyran (VII) may be isolated by treatment of the molecular distillation residue with aqueous sodium chloride and carbon dioxide. This 91 per cent yield of (VII) may be compared with approximately equal (20 per cent) yields of (VII) and 2,6-dimethyl-3-chloromercuriheptane-2,6-diol (VIII) that are obtained when dimethylheptenol is treated with mercuric acetate in water. This behavior may be explained if the (second-order) rate-controlling step is presumed to be the formation of hydroxymercuric acetate or else of the basic salt (IX), either of which may then add to the alkene to give the actual products.

On the other hand, it is difficult to reconcile this behavior with an ionic mechanism of reaction. First, it would not be expected that a tertiary alcohol or its alkoxide ion, which would be required in an ionic scheme of reaction, would possess activity comparable to that of water or a hydroxyl ion. Second, one might expect that ionic species would be more prevalent in aqueous media than in dimethylheptenol, but yields are higher in the unsaturated alcohol than they are in water. Last, it might be predicted on the basis of an ionic mechanism involving a salt such as mercuric acetate (derived from a weak base and a weak acid) that the addition of acetic acid initially would increase the rate of an ionic reaction by reducing solvolysis. It may be seen from FIGURE 3 that acetic acid reduces the rate.

In short, the present evidence seems to favor the intermediacy of a basic mercuric salt in the oxymercuration reaction.

Earlier it was stated that, when geoisomeric alkenes are oxymercurated, each form gives a specific diastereomer. When the geoisomers can be designated as *cis* and *trans* (that is, when R_1 and R_2, structure I, are hydrogen), then the oxymercurial arising from the *cis* alkene is designated as *alpha*, and the other is *beta*. The oxymercurials formed from 5- and 6-atom cycloalkenes are also designated as *alpha* diastereomers.

When an organomercury salt is treated with a reducing agent, the first stage of the reaction undoubtedly produces a free radical;[19] if sufficient reducing potential is available, this radical combines with a hydrogen atom to form the corresponding alkane

$$\mathrm{RHgCl} \xrightarrow{\mathrm{H}^{\cdot}} \mathrm{Hg} + \mathrm{HCl} + \mathrm{R}^{\cdot} \xrightarrow{\mathrm{H}^{\cdot}} \mathrm{R{-}H} \tag{6}$$

The equivalent of this situation exists with sodium amalgam in water. The earlier statement that such a reaction proceeds with loss of configuration in the *R* group is understandable on the basis of the radical type of reaction.

Several alternative radical processes seem to be operative with homogeneous reducing agents such as sodium stannite or hydrazine, as shown in FIGURE 4. The ratios of the dialkylmercury, dialkyl, and the alkane-alkene disproportionation products depend on the individual mercurial compound as well as on the reducing agent. Any specific stereochemical configuration of the *R* group is always lost, however, as one might expect if the reactions involved radicals.

A typical example of this reduction is shown below for the treatment of α-2-methoxycyclohexylmercuric chloride (X) with hydrazine in FIGURE 5.

It may be seen that, besides the alkene (XIII) and the alkane [(XIV) de-

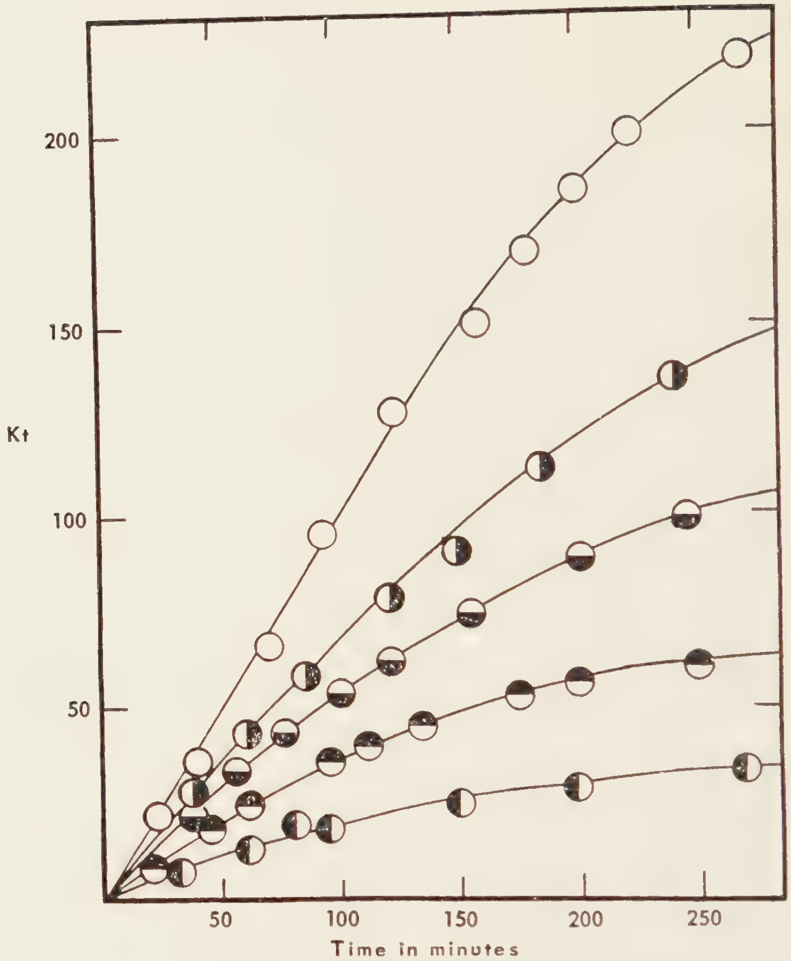


FIGURE 3. The reaction between mercuric acetate (4.0×10^{-3} mol/liter) and dimethyl heptanol (4.0×10^{-3} mol/liter) in 1,2-dimethoxyethane with added acetic acid at 25.0 ±0.1° C.

Legend: Acetic acid ○ none, ◑ 2.0×10^{-3} mol/liter; ◒ 8.0×10^{-3}; ◓ 16.0×10^{-3} mol/liter.*

* Reproduced by permission of the *Journal of Applied Chemistry.*

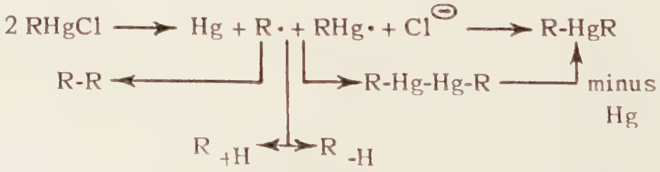


FIGURE 4*

Reproduced by permission of *Chemistry in Canada.*

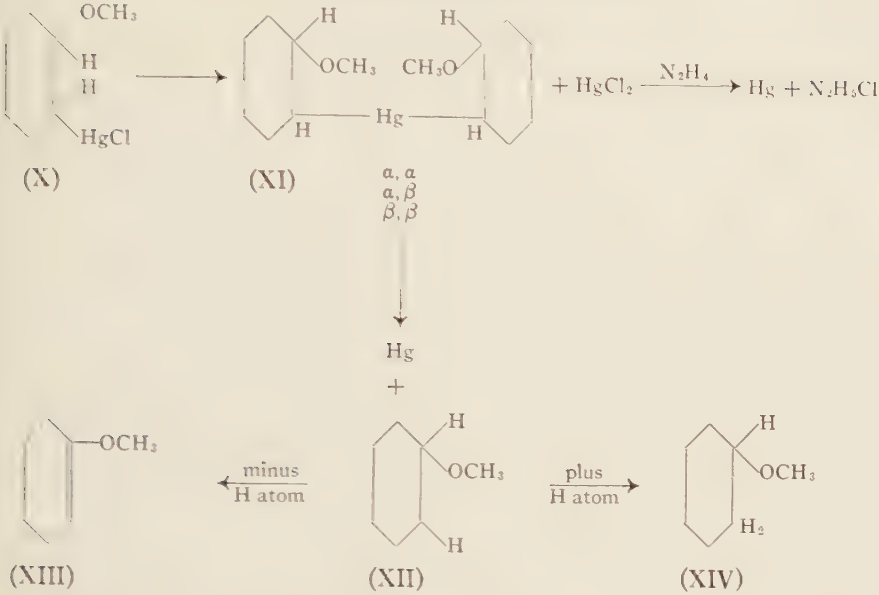
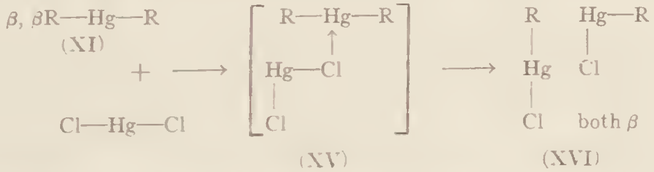


FIGURE 5*

rived by disproportionation of the radical (XII)], a mixture of 3 diastereomeric *bis*-mercurials (XI) is formed. In this case it is found that the α-α and α,β-*bis*-mercurials (XI) are thermally unstable, and that only the β,β-*bis*-mercurial (XI) survives repeated distillation. When this β,β-*bis*-mercurial is treated with mercuric salt, the reaction is found to be stereospecific, and only the β-2-methoxycyclohexylmercuric salt (XVI) is obtained as a product. In consequence of this stereospecificity the reaction is depicted as proceeding via the intermediate (XV). These reactions are shown in EQUATION 7.

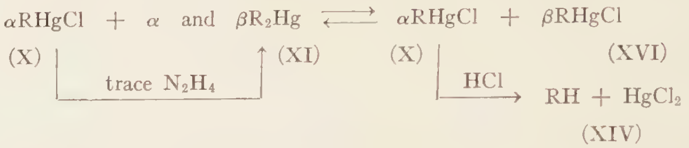

(7)

$$\begin{matrix} \beta,\beta\text{R—Hg—R} \\ \text{(XI)} \\ + \\ \text{Cl—Hg—Cl} \end{matrix} \longrightarrow \left[\begin{matrix} \text{R—Hg—R} \\ \uparrow \\ \text{Hg—Cl} \\ | \\ \text{Cl} \end{matrix}\right]_{\text{(XV)}} \longrightarrow \underset{\text{(XVI)}}{\begin{matrix} \text{R} & \text{Hg—R} \\ | & | \\ \text{Hg} & \text{Cl} \\ | & \\ \text{Cl} & \text{both } \beta \end{matrix}} \qquad (7)$$

The comparative stabilities of the α and β methoxycyclohexyl *bis*-mercurials (XI) extend also to the 2-methoxycyclohexylmercuric salts, the β form (XVI) being much more stable toward mineral acid than is the α form (X). Therefore, if α-2-methoxycyclohexylmercuric chloride can be converted to an α,β mixture, the α form can be destroyed by quick treatment with hydrochloric acid, leaving the almost pure β form. The conversion to the mixture can be accomplished by treatment of the α salt with a trace of hydrazine hydrate, thus creating a small amount of *bis*-mercurial (XI) which enters into the equilibrium shown in EQUATION 8, while subsequent treatment with hydrochloric acid leaves only β-2-methoxycyclohexylmercuric chloride which, of course, can be decomposed by very strong hydrogen chloride to give the alkene.

---

* Reproduced by permission of the *Canadian Journal of Chemistry*.



$$\underset{(X)}{\alpha\text{RHgCl}} + \alpha \text{ and } \underset{(XI)}{\beta\text{R}_2\text{Hg}} \rightleftarrows \underset{(X)}{\alpha\text{RHgCl}} + \underset{(XVI)}{\beta\text{RHgCl}} \qquad (8)$$

$$\underset{(X)}{\alpha\text{RHgCl}} \xrightarrow{\text{trace } N_2H_4} \underset{(XI)}{\beta\text{R}_2\text{Hg}} \qquad \underset{(X)}{\alpha\text{RHgCl}} \xrightarrow{\text{HCl}} \text{RH} + \underset{(XIV)}{\text{HgCl}_2}$$

Since only 1 cyclohexene exists, it is evident that both diastereomers in the example described above must give the same alkene. However, in instances where geometric alkenes are existent, the hydrogen-chloride demercuration of their mercurials gives the alkene from which the mercurial was derived, or could have been derived if it had not been produced indirectly by the isomerization described above. It is evident that this chemistry provides a method for conversion of one geoisomer into the other, and this has been accomplished by the reaction series shown in FIGURE 6, where *trans*-stilbene (XVII) is converted to *cis*-stilbene (XVIII).

The reader will at once detect a contradiction in this exposition. Since *trans*-stilbene, by definition, gives the β-diastereomeric oxymercurial (XIX), it might be expected, by analogy with the β-2-methoxycyclohexylmercuric chloride, to be the isomer that would survive mild treatment with hydrogen chloride, but the converse is the fact. Evidently an orientation factor, impossible with the ring-bound 2-methoxycyclohexylmercuric salts, has operated to make the oxymercurial (XIX) from *trans*-stilbene less stable toward hydrogen halide than the corresponding oxymercurial (XX) from *cis*-stilbene. This

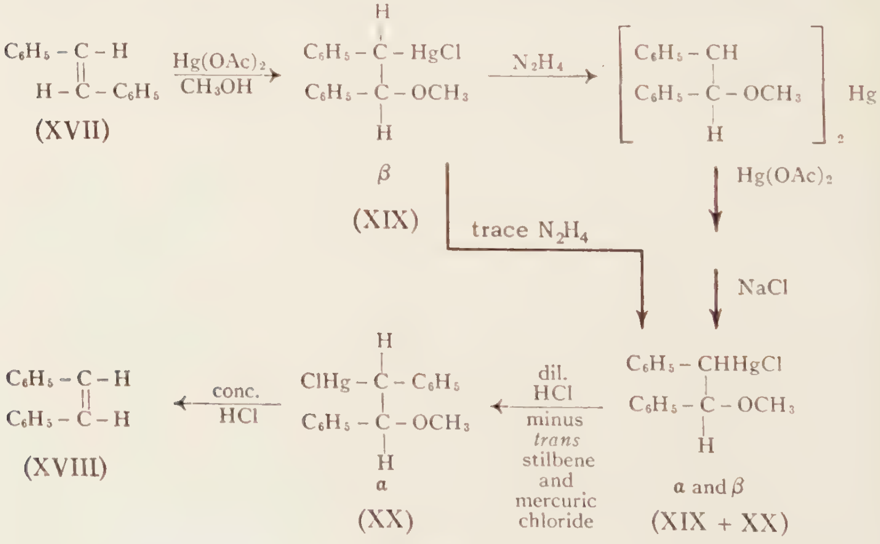


FIGURE 6*

---

* Reproduced by permission of the *Canadian Journal of Chemistry.*

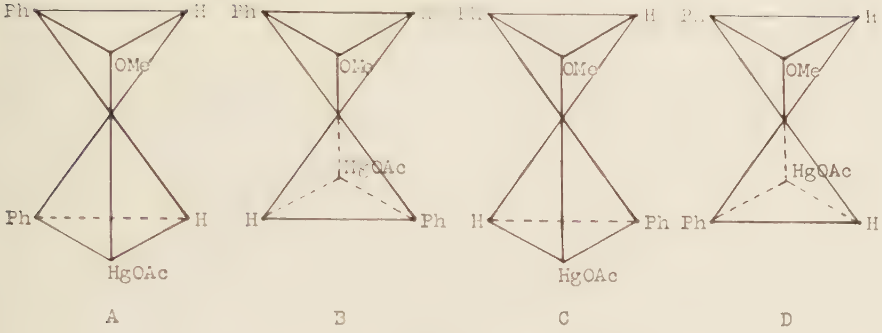


FIGURE 7

orientation factor must have occurred subsequent to the formation of the 2-methoxy-1,2-diphenylethylmercuric salt because *cis*-stilbene is oxymercurated much more rapidly than the *trans* geoisomer. If the conversion by acid of an oxymercurial to the alkene can be considered to be a reversal of the formation of the oxymercurial from that alkene, then the constellation of atoms must have changed by rotation at the pivotal bond in the 2-methoxy-1,2-diphenylethylmercuric salt diastereomers.

Thus, referring to FIGURE 7, *A* and *B* represent opposite constellar arrangements of one diastereomer, while *C* and *D* represent the other diastereomer. If mass symmetry is a criterion for the probability of existence of these 4, then the order of probability is $B > C > D > A$. It seems reasonable to presume that the constellations from which *trans*-stilbene would be regenerated would be *B* or *C*, depending upon whether the elimination of methoxy- and acetoxymercuri were "trans" (with Walden inversion) or "cis" (without inversion). If elimination and, since oxymercuration is reversible, the over-all addition, were "trans," however, then the methoxymercuration of *cis*-stilbene should lead initially to constellation *D*, in which the phenyl groups were contiguous. An escape from this contiguity would lead to constellation *C*, which would be little more favorable because of the contiguity of methoxyl and acetoxymercuri. Such a mechanism does not provide a convincing explanation for the fact that *cis*-stilbene methoxymercurates more easily than the *trans* geoisomer, while the resulting methoxymercurial is more difficult to "deoxymercurate" than the methoxymercurial from *trans*-stilbene.

On the other hand, the apex-apex (*cis*) addition of the element of methoxymercuric acetate (III) to *cis*-stilbene would form constellation *A*, which ought to rotate pivotally into *B* for lowest energy and thus would be conformed unfavorably for deoxymercuration. *Trans*-stilbene ought to add (*cis*) the elements of methoxymercuric acetate, however, and form constellation *C*, a form favorable for deoxymercuration from the aspect of phenyl-group noncontiguity. Therefore, *cis* addition seems to be more reasonable than *trans* addition as an explanation for the oxymercuration of alkenes.

An apparent contradiction of this mechanism, however, appears in single-crystal X-ray diffraction studies of the α and β-2-methoxycyclohexylmercuric chlorides. Complete structure determinations on 3 projections for each of

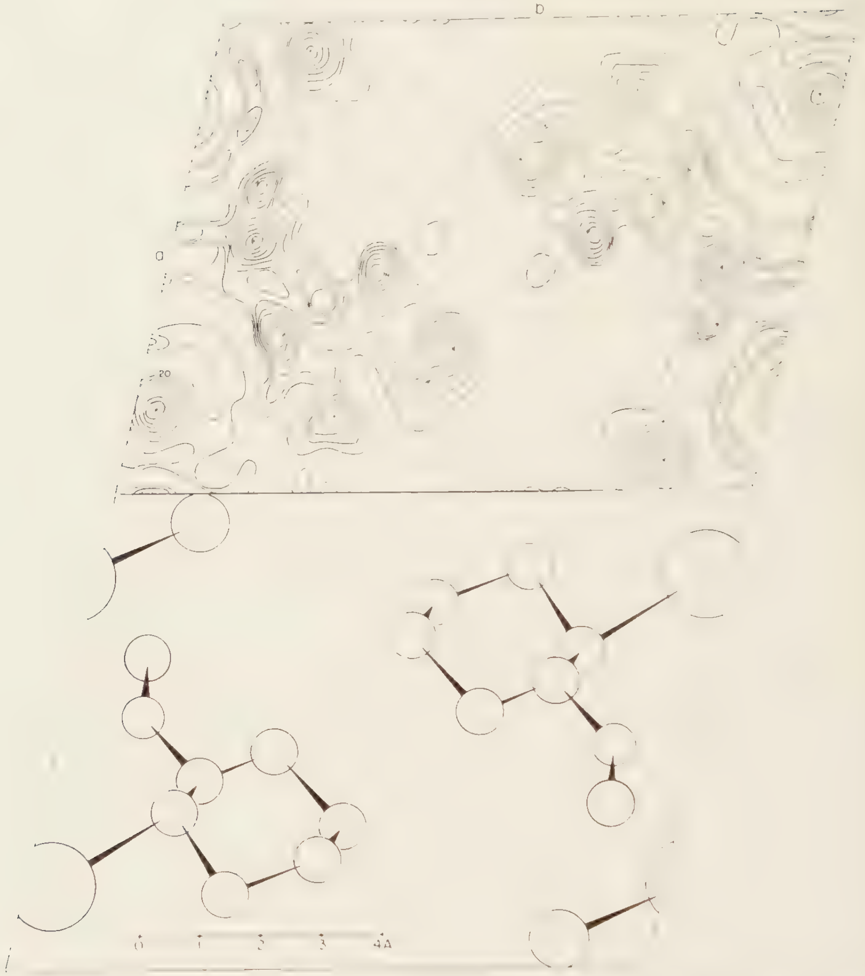


FIGURE 8. Below: idealized projection of the α-diastereomer (X) derived from the electron-density contour map above.*

* Reproduced by permission of *Chemistry in Canada*.

these diastereomers show that the α form obtained by methoxymercuration of cyclohexene has the configuration that would be the result of *trans* addition.

The lower part of FIGURE 8 shows an idealized projection of the α-diastereomer (X), derived from the electron-density contour map shown in the upper part of the same figure.

The contour maps obtained by Fourier synthesis of the structure factors derived from moving-film photographs of β-2-methoxycyclohexylmercuric chloride reflexions show about the same correlation, $\Sigma^n \mid F_{\text{obs.}} \mid - \mid F_{\text{calc.}} \mid / \Sigma^n \mid F_{\text{obs.}} \mid$ (13.4 per cent) as does the α-diastereomer (9.9 per cent). This study designates the β diastereomer, which is derived by isomerization of the α form, and not by oxymercuration of cyclohexene, as having the methoxy and chloromercuri groups in the contiguous (*cis*) relationship.

While these X-ray studies would seem to render questionable the conclusions drawn with respect to the methoxymercuration of the stilbenes, it must be remembered that X-ray study is not as exact a technique as a brief acquaintance with it would indicate. For example, one must remember that the all-important crown constellation of the cyclohexane ring *was assumed* for these structure calculations. However, the high (97) electron contributions of mercury and chlorine, which are largely responsible for the acceptable (10 to 13 per cent) correlation values, tend to reduce the reliability of positioning the 6-electron carbon atoms in the constellation. Thus the reliability of the entire proof of structure is more apparent than real.

One might seek a solution to this quandary by supposing that there were 2 modes of oxymercurial addition, one of which applied to cyclohexene and the other to stilbene. This supposition is unlikely. Among a large number of alkenes that have been oxymercurated, only 1 diastereomer has been obtained from each geoisomer. One would certainly have expected to have encountered a borderline instance where both mechanisms were operative, if 2 existed. Moreover, among all diastereomeric oxymercurials, those from cyclohexene and the stilbenes included, the form that is the most difficult of deoxymercuration always has the highest electric moment. This feature would imply that such substances are structurally related.

In view of the apparent contradiction outlined above, a different criterion has been sought and found. The oxymercuration of 1,4-↑↑-methylene-5-cyclohexene-2.3-↓↓-dicarboxylic acid (μ, 2.43, FIGURE 9) may be oxymercurated in aqueous mercuric acetate to give monomeric 5-↓-hydroxy-anhydro-[6-↓-hydroxymercuri-2-↓-carboxy]-1,4-↑↑-methylenecyclohexane-3-↓-carboxylic acid, γ-lactone, whose molecular weight is 382. This substance, which certainly must have its substituent groups in the contiguous (*cis*) position, may be converted by sodium chloride and dilute hydrochloric acid to 5-hydroxy-6-↓-chloromercuri-1,4-↑↑-methylenecyclohexane-2,3-↓↓-dicarboxylic acid, γ-lactone, whose electric moment is 3.88. Alternatively, if the anhydrolactone, whose molecular weight is 382, is treated, as described earlier in this paper, with a reducing agent (sodium stannite), a mixture of diastereomers is formed. One of them reverts to the parent anhydrolactone when mildly acidified with acetic acid. The other (rearranged) β-diastereomer, upon acidification with hydrochloric acid, becomes 5-↓-hydroxy-6-↑-chloromercuri-1,4-↑↑-methylenecyclohexane-2,3-↓↓-dicarboxylic acid, γ-lactone, with the high electric moment of 7.18. Prototropic rearrangement of the nonlactonized carboxyl group in this β-mercurial produces 5-↓-hydroxy-6-↑-chloromercuri-1,4-↑↑-methylenecyclohexane-2-↑-3-↓-dicarboxylic acid, γ-lactone, $\mu = 5.60$ *D*. Likewise the α-chloromercurial, $\mu = 3.88$, may be prototropically rearranged to 5-↓-hydroxy-6-↓-chloromercuri-1,4-↑↑-methylenecyclohexane-2-↑-3-↓-dicarboxylic acid, $\mu = 4.53$. These prototropically rearranged acids can be deoxymercurated to 1,4-↑↑-methylene-5-cyclohexene-2,3-↑↓-dicarboxylic acid ($\mu = 2.19$ *D*). This latter acid can be oxymercurated to give the mercurial of electric moment 5.60 *D* in what seems to be an exception to the concept of contiguous (*cis*) oxymercura-

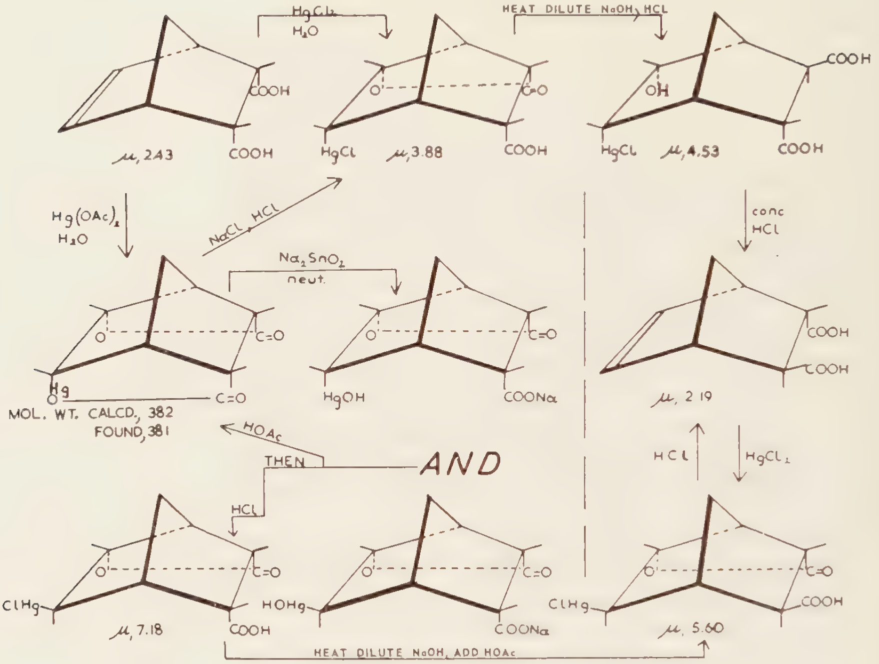


FIGURE 9

tion. This is "the exception that proves the rule," however, because all norbornenes that have been oxymercurated have given diastereomeric forms that are opposite to those encountered with ordinary alkenes. This abnormality is expected in view of the behavior of norbornenes toward bromine[20] and hydroxyl addition. Probably, 1,4-$\uparrow\uparrow$-methylene-5-cyclohexene-2,3-$\downarrow\downarrow$-dicarboxylic acid (μ 2.43) behaves as the common alkenes do because the intermediate mercuric salt that it forms is spatially favorable for contiguous addition to the double bond. Rapid reaction would preclude 1,2-rearrangement.

Like diastereomeric oxymercurials in general, the β isomers, $\mu = 7.18$ *D* and $\mu = 5.60$ *D*, are more difficult to deoxymercurate than is the α series, $\mu = 3.88$ and $\mu = 4.53$. Since the positions of the oxy and mercuri groups in these substances are known, and since it has been shown that the esters and ethers of oxymercurials are configurationally related[21] as shown in FIGURE 10, the con-

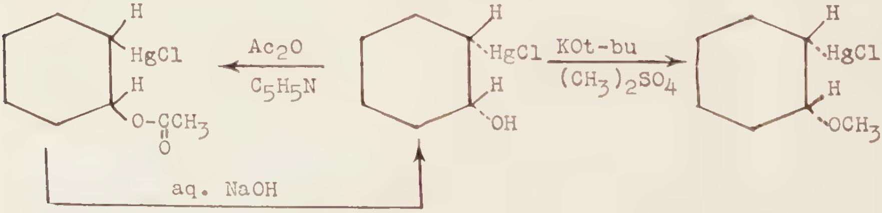


FIGURE 10

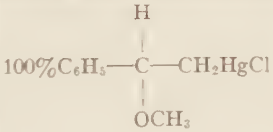
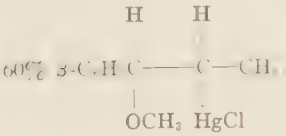
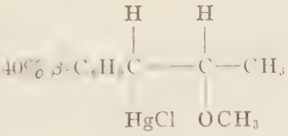
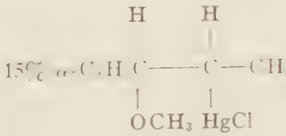
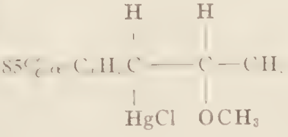
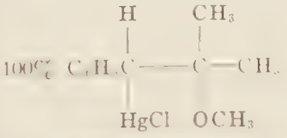
figuration of α oxymercurials would seem to be defined as a result of contiguous (*cis*) addition except for the specific and predictable exceptions noted among other norbornenes. The X-ray diffraction study must then be considered to be nondefinitive and, until contrary evidence is forthcoming, this contiguous addition is accepted as the rule.

This designation of oxymercuration as a reaction involving coaddition of molecular (nonionic) species must imply that the steric and polar attributes of the alkenes should affect the oxymercuration profoundly. This expectation is borne out by a study of laterally methylated styrenes.[6] The products obtained from styrene, *cis* and *trans* propenylbenzenes (β-methylstyrenes) and β,β-dimethylstyrenes are shown in TABLE 1.

The minimum of double-bond polarization in the propenylbenzenes is apparent in the formation of positional isomers that are not obtained from the more polar styrene and β,β-dimethylstyrene. Of interest in relationship to this polarization are the relative rates of reaction. The oxymercuration of styrene is so rapid that it cannot be included demonstrably in FIGURE 11. It will be seen that β,β-dimethylstyrene is next in reactivity, followed by *cis* and, finally, by the least active *trans* propenylbenzene. This behavior is not unex-

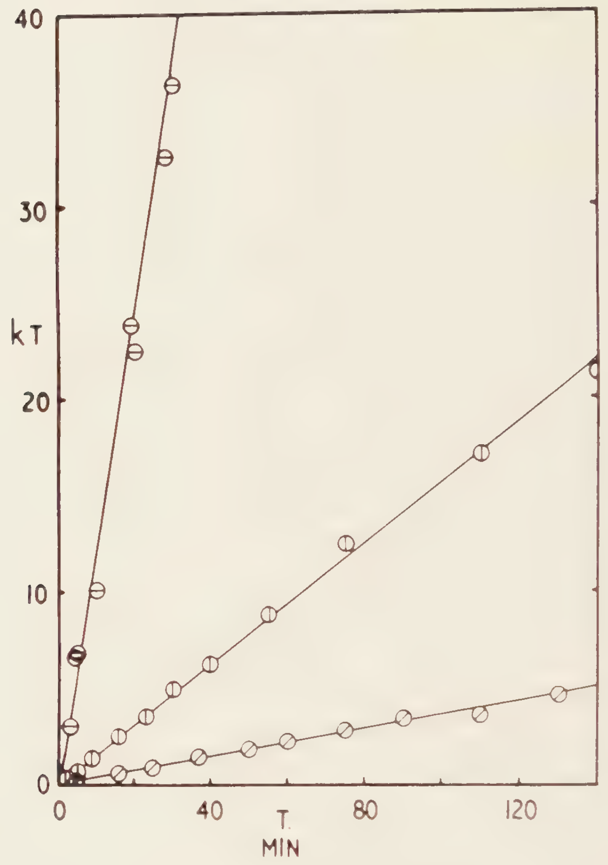
TABLE 1*

METHOXYMERCURATIONS OF STYRENES

Substance	Mercuration products and yields	
Styrene	 $100\%\,C_6H_5-\underset{OCH_3}{\overset{H}{C}}-CH_2HgCl$	
trans-Propenylbenzene	 $60\%\ \beta\text{-}C_6H_5\underset{OCH_3}{\overset{H}{C}}-\underset{HgCl}{\overset{H}{C}}-CH_3$	 $40\%\ \beta\text{-}C_6H_5\underset{HgCl}{\overset{H}{C}}-\underset{OCH_3}{\overset{H}{C}}-CH_3$
cis-Propenylbenzene	 $15\%\ \alpha\text{-}C_6H_5\underset{OCH_3}{\overset{H}{C}}-\underset{HgCl}{\overset{H}{C}}-CH_3$	 $85\%\ \alpha\text{-}C_6H_5\underset{HgCl}{\overset{H}{C}}-\underset{OCH_3}{\overset{H}{C}}-CH_3$
2-Methyl-1-phenyl-2-propene		 $100\%\ C_6H_5\underset{HgCl}{\overset{H}{C}}-\underset{OCH_3}{\overset{CH_3}{C}}-CH_3$

---

* Reproduced by permission of the *Journal of Organic Chemistry.*



RATE OF METHOXYMERCURATION

	K	k-MIN^{-1}	CONC.
⊖ 1-PHENYL-2-METHYLPROPENE-1	10	116	0.1M
⦶ CIS-PROPENYLBENZENE	3.5	0.157	0.1M
⊘ TRANS-PROPENYLBENZENE	32	0037	01M

FIGURE 11*

pected on the basis of the molecular addition of molecular methoxymercuric acetate to these alkenes.

It may be seen that the stereochemical integrity of the oxymercuration provides a useful device in the study of spatial organic chemistry. This feature is realized further in a reaction that organomercurials undergo with excess of mercuric salts, by which the mercury is reduced to the (I) state while the or-

---

* Reproduced by permission of the *Journal of Organic Chemistry.*

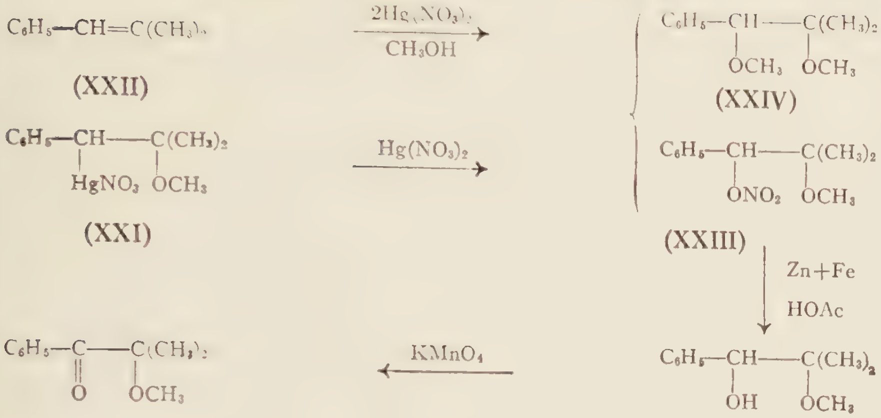


FIGURE 12*

* Reproduced by permission of the *Canadian Journal of Chemistry.*

ganic moiety is oxidized.[5] Typical is the reaction of benzylmercuric nitrate with mercuric nitrate in methanol, which yields mercurous nitrate, benzyl methyl ether, and benzyl nitrate. When this reaction is carried out in water, benzyl nitrate is still a product.[22] This unusual circumstance of the formation of a nitrate ester in aqueous solution is likewise displayed in the oxidation of 2-methoxy-2-methyl-1-phenylethyl mercuric nitrate (XXI) by mercuric nitrate. This reaction may be carried out either with β,β-dimethylstyrene (XXII) or its mercurial, because the oxymercuration is much faster than the oxidation-reduction. In methanolic medium, as is shown in FIGURE 12, the products are 1,2-dimethoxy-1-methyl-2-phenylpropane (XXIV) and 2-methoxy-2-methyl-1-phenylpropyl nitrate (XXIII), the structure of the latter being demonstrated by reduction and oxidation as shown. This same nitrate ester, however, is also produced in aqueous medium. The suspicion is thus aroused that this oxidation-reduction proceeds via free nitroxy and methoxy radicals, and it is confirmed by the demonstration that butylmercuric nitrate, which will not react in methanol with mercuric nitrate, is partly converted to butyl methyl ether when a hydroxyl radical source such as Fenton's reagent is included in the system.

Of great interest is the observation that this radical replacement of the nitratomercuri group by methoxy or nitroxy radicals is at least 95 per cent stereospecific, and probably completely so. This characteristic feature of the reaction is exemplified by the treatment of *cis*-and *trans*-stilbene with 2 equivalents of mercuric nitrate. This is equivalent to the treatment of the 2-methoxy-1,2-diphenylethylmercuric chloride diastereomers with equivalent amounts of mercuric nitrate, because oxymercuration is much more rapid than the oxidation-reduction. The various diastereomeric di-ethers and ether nitrates obtained as products are shown below, together with the nonstereospecific 1,2-rearrangement product, diphenylacetaldehyde (XXV), which is produced from both diastereomeric oxymercurials of the stilbenes. The stereochemical structure proofs, which depend on the known configurations of the 1,2-di-

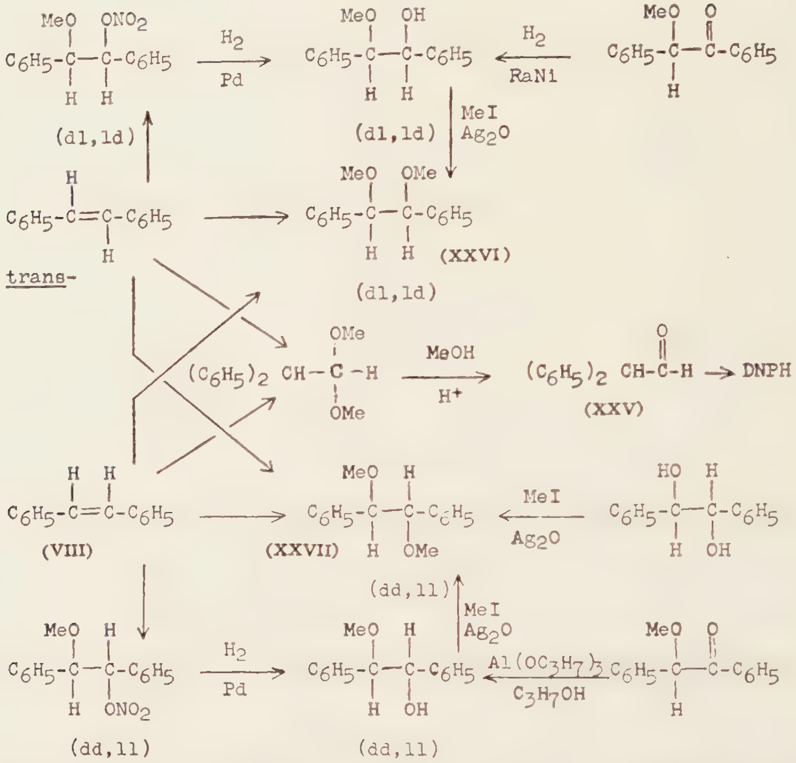


FIGURE 13. The products listed below are arranged in the order in which they are separated from an alumina column by frontal displacement:

From *cis*-stilbene			From *trans*-stilbene
cis	(1)	stilbene	*trans*
dd,ll	(2)	2-methoxy-1,2-diphenylethyl nitrate	*dl,ld*
dl,ld	(3)	1,2 dimethoxy 1,2 diphenylethane	*dl,ld*
	(4)	diphenylacetaldehyde dimethylacetal	
dd,ll	(5)	1,2-dimethoxy-1,2-diphenylethane	*dd,ll*

methoxy-1,2-diphenylethanes (XXVI and XXVII), also are outlined briefly in FIGURE 13.

If the configurations of the oxymercurials are those resulting from contiguous (*cis*) addition to the geoisomeric stilbenes, then these oxidation products (the diethers and ether nitrates) must have been formed by the back-to-side approach of nitroxy and methoxy radicals. This radical replacement by Walden inversion is unique.

In summary, the formation and reactions of oxymercurials derived from alkenes provide criteria that contribute largely to the knowledge of molecular addition reactions. The observed facts cannot be said to be completely or, perhaps even correctly, interpreted. Indeed, there are other opinions about oxymercuration that have not been described in this paper[23] and that are contrary to the opinions expressed here. These other opinions are worthy of consideration if they are applied to the facts of oxymercuration, part of which are outlined in the present report.

References

1. Hofmann, K. A. & J. Sand. 1900. Ber. deut. chem. Ges. **33:** 1340.
2a. Manchot, W. 1920. Ber. deut. chem. Ges. **53B:** 984.
2b. Manchot, W. 1920. Ann. Chem. Justus Liebigs. **420:** 170.
3a. Adams, R., F. L. Roman & W. N. Sperry. 1922. J. Am. Chem. Soc. **44:** 1781.
3b. Adams, R. & L. E. Mills. 1923. J. Am. Chem. Soc. **45:** 1842.
4a. Sandborn, L. T. & C. S. Marvel. 1926. J. Am. Chem. Soc. **48:** 1409.
4b. Griffith, E. & C. S. Marvel. 1931. J. Am. Chem. Soc. **53:** 789.
5. Shearer, D. A. & G. F. Wright. 1955. Can. J. Chem. **33:** 1002.
6. Park, W. R. R. & G. F. Wright. 1954. J. Org. Chem. **19:** 1435.
7a. Biilmann, E. 1902. Ber. deut. chem. Ges. **35:** 2571.
7b. Biilmann, E. 1910. Ber. deut. chem. Ges. **43:** 568.
8. Wright, G. F. 1935. J. Am. Chem. Soc. **57:** 1993.
9. Connor, T. & G. F. Wright, 1946. J. Am. Chem. Soc. **68:** 256.
10. Brown, W. H. & G. F. Wright. 1940. J. Am. Chem. Soc. **62:** 1991.
11a. Sand, J. 1902. Ber. deut. chem. Ges. **35:** 3170.
11b. Sand, J. 1903. Ann. Chem. Justus Liebigs **329:** 135.
12. Nesmeyanov, A. N. & R. K. Freidlina. 1936. Ber. deut. chem. Ges. **69:** 1631.
13. Freidlina, R. K., A. N. Nesmeyanov & F. Takavera. 1936. Ber. deut. chem. Ges. **69:** 2019.
14. Sand, J. 1901. Ber. deut. chem. Ges. **34:** 2906.
15. Hugel, G. & J. Hibou. 1929. Chimie & industrie, Special No. : 296.
16. Brook, A. G. & G. F. Wright. 1950. Can. J. Research. **B28:** 623.
17. Freidlina, R. K. & N. S. Kochetkova. 1945. Bull. acad. sci. URSS Classe sci. chim. : 128.
18. Brook, A. G., A. Rodgman & G. F. Wright. 1952. J. Org. Chem. **17:** 988.
19. Wright, G. F. 1952. Can. J. Chem. **30:** 268.
20. Berson, J. A. 1954. J. Am. Chem. Soc. **76:** 4069.
21. Park, W. R. R. & G. F. Wright. Unpublished.
22. Robson, J. H. Ph.D. Thesis. To be published. Univ. Toronto. Toronto, Canada.
23. Chatt, J. 1951. Chem. Revs. **48:** 7.

A PHYSICOCHEMICAL RATIONALE FOR THE BIOLOGICAL ACTIVITY OF MERCURY AND ITS COMPOUNDS[*]

By Walter L. Hughes
Brookhaven National Laboratory, Upton, N. Y.

The biological effect of mercury has been found to vary according to the nature of the chemical compound administered. I propose to develop the concept that in all cases the principal reaction is with thiols (that is, the formation of mercury mercaptide) and that the variations in distribution and effect are dependent upon this reaction. This is not a new concept; the affinity of mercury for sulfur was known to the alchemists. However, since the extreme specificity of this reaction is sometimes lost sight of today, it should be documented.

Mercury exists in a variety of chemical compounds, including mercurous and mercuric salts and a wide variety of organic mercurials, as well as metallic mercury. For the purposes of this discussion I should like to begin with what is chemically the simplest mercury compound, the alkyl mercuric halide, CH_3HgBr. It will be seen that this compound possesses both a stable carbon-mercury bond and the essentially ionic mercury-halogen bond. Carbon mercury bonds possess a wide range of stabilities. In general, aliphatic carbon combines more stably with mercury than aromatic carbon; however, both would appear sufficiently stable to resist usual physiological processes.[†] Therefore, the pharmacology of methylmercury halides may be discussed in terms of the affinity of the methylmercury ion for biological substances. This affinity may be described by the following equation

$$CH_3Hg^+ + X^- = CH_3HgX$$

Relative affinities for various biological substances may then be obtained by comparing the equilibrium constants for this reaction

$$K = \frac{[CH_3HgX]}{[CH_3Hg^+][X^-]}$$

I have measured a few of these equilibrium constants[‡] and the values obtained are given in TABLE 1 as the logarithm of the association constant. From the magnitudes of these association constants it will be seen that the methylmercury ion can exist only in infinitesimal concentrations in biological solutions. Thus at *p*H 7 there must be 500 times as much methylmercury hydroxide as methylmercury ion. Moreover, if chloride is also present at physiological concentrations (that is, 0.1M), then there must be 100 times as much methylmercury chloride as methylmercury hydroxide. However, since all biological systems

---

[*] The work described in this paper has been supported by the United States Atomic Energy Commission, Washington, D. C.

[†] George F Wright in the preceding article has discussed addition reactions of mercuric salts to some unsaturated compounds, which are readily reversible These compounds presumably also would reverse under physiological conditions.

[‡] The method that involves measuring the equilibrium distribution of the reactants between aqueous and organic solvents has been briefly described.[2]

TABLE 1

ASSOCIATION CONSTANTS OF METHYLMERCURY FOR CERTAIN LIGANDS

Ligand	RS^-	OH^-	I^-	Br^-	Cl^-
$\log_{10} K$	17	9.7	9.0	7.0	5.7

TABLE 2

EQUILIBRIUM CONSTANTS OF METHYLMERCURY IODIDE FOR SEVERAL PROTEINS

Protein	$K \times 10^6$
Human serum albumin	25
Bovine serum albumin	7
Bovine oxyhemoglobin	20
Bovine carbonylhemoglobin	6

contain thiols, the extremely large association constant for this reaction must mean that all but traces of the mercurial will be bound to thiols, provided that they exceed the amount of mercury present.* Certainly this is usually the case; human blood plasma, for example, is 0.5 millimolar in thiol,[1] and the accompanying red cells contain 60 times as much sulfhydryl in their hemoglobin. Thus a man's blood plasma alone should be able to combine with 1½ mMol of mercurial containing 300 mg. of mercury, an amount far in excess of a pharmacological dose.†

The association constant of methylmercury mercaptide given in TABLE 1 is that for human serum albumin. In calculating this value it was assumed that the competing protons have an affinity constant for this thiol of $\log_{10} = 10$. Association constants have been measured for bovine serum albumin and for two derivatives of bovine hemoglobin.[3] These values are given in TABLE 2 in the form of equilibrium constants for the reaction

$$CH_3HgI + Prot \cdot SH = CH_3HgS \cdot Prot + H^+ + I^-$$

(where Prot·SH represents the protein sulfhydryl groups)

It will be noted that even among these closely related proteins there is a marked variation of association constant from species to species and from derivative to derivative. Even larger differences presumably exist in the body. The presence of thiols with higher affinity constants for mercury is suggested by the behavior of iodoacetate, another sulfhydryl poison. Thus iodoacetate has been shown to inactivate sulfhydryl enzymes by alkylating their sulfhydryl groups[4] under physiological conditions, where it is inert toward the sulfhydryl of serum albumin.

---

* If the thiol is present in millimolar concentration and has an acid association constant $\log_{10}$ of 10 then at pH 7 the ratio of methylmercury mercaptide to methylmercury chloride will be 2,000,000:1 (i.e., proportional to the affinity constants times the concentrations of the reactants: $(10^{17} \cdot 10^{-3} \cdot 10^{-3})/(10^{5.7} \cdot 10^{-1})$).

† Methylmercury also shows strong affinities for many other groupings present in biological substances. As precise values for these are not known, however, they were not included in the table. I have estimated the affinity of methylmercury for carboxyl groups as log K = [illegible]. The affinity for amide and amine [illegible] probably of the same order of magnitude or somewhat larger. Thus in isolated protein systems and in the absence of halides, extremely large amounts of methylmercury may be bound. In this way I have bound up to 100 mol of methylmercury to 1 mol of serum albumin.

TABLE 3
MERCURY CONTENT OF HUMAN TISSUES

Mercury compound absorbed	Dose or period of exposure	Interval between last exposure and death	Mercury content of tissues in parts per million							
			Kidney	Liver	Brain	Spleen	Lungs	Heart	Blood	Reference
CH_3HgX	"chronic"		30	19	5		3			Ahlmark[11]
	5 yr.	1 mo.	3	14	4–9	4	2		4*	Lundgren and Swennson[12]
Mercaptomerin†									Serum	
	40 mg.	0.4 day	9	1.8	0.2	0.9	1.7	0.8	2.8	Aikawa and Fitz[13]
	80 mg.	1.5 day	12	5		6	8	1.4	5.4	
	80 mg.	2 day	17	1.8		0.6	1.3		0.9	
	80 mg.	6 day	5	0.6	0	0.3	0.2	0.1	0.3	
Mercuric Salts										
$Hg(\phi COO)_2$	Inunction	37 day	63	12	1.5	6	1	3.7	(1.1)‡	Lomholt[14]
$HgCl_2$	Acute poisoning	3 day	70	32	1.7	10	6	3		
		6 day	16	3	1.0	4	.3	2.4		
$HgCl_2$	2.5 gm.	6 day	35	25					1	Sollmann and Schreiber[15]
	5.5 gm.	9 day	33	26					1.2	
	1 gm.	8 day	24	10					0.1	
Metallic vapor	19 yr.	6 mo.	21	28	9	1.5				Brigatti[16]
	7 yr.	12 mo.			6–7	.6				
	8 mo.	?	26	9	0–0.9			2.3		

* Blood taken day before death

† Camphoryl ($C_{10}H_{15}O_3$) $NH \cdot CH_2 \cdot CH(OCH_3) \cdot CH_2 \cdot Hg \cdot SCH_2 \cdot COOH$

‡ Median value obtained by Lomholt for similar inunction treatments

As regards the other mercurials, it will be obvious that one can modify still further the relative affinity of the mercurial for various sulfhydryl compounds by replacing the methyl group by other larger organic radicals and by organic radicals containing other functional groups. Thus in the first place one might expect interference from a large grouping if the sulfhydryl group were located in a "tight" part of the protein molecule or if there were charges on groups adjoining the sulfhydryl group and if the mercurial carried an identical charge.

Conversely, of course, if the mercurial carried the charge opposite to that of the region surrounding the sulfhydryl group, the affinity constant should be increased. Similarly, after binding to sulfhydryl, the mercuric ion still contains a free valence capable of combining with some other properly placed group. Thus, in general, mercuric ions should bind more tightly than simple mercurials, and considerable variation in affinity should exist from protein to protein. Carrying this argument still further, it seems possible that mercurials exist, or could be produced, containing groupings spatially similar to the substrate molecule normally reacting where the mercurial is bound. In this way a second bond would be provided, and the association constant might be increased by an amount typical of competitive enzyme inhibitors ($\log_{10}K \sim 3$), permitting still greater specificity for the site of action of the mercurial. It is perhaps worth stressing again that all of these interactions are small, relative to primary mercaptide formation. Therefore, they can direct the mercurial only to certain thiols, but never away from thiols.

Thus far we have limited our discussion to homogeneous systems. In the living organism numerous barriers to mixing exist, and we should therefore consider the problems of diffusion and transport. First, it has been pointed out that the blood is sufficiently rich in thiols to permit binding of large amounts of mercurial that can thus be transported to all regions of the body. Most of the thiols of human plasma can be accounted for by serum mercaptalbumin containing 1 thiol group per protein molecule. However, 5 to 10 per cent of the total thiol content of human plasma is present in the form of small molecules.[1] Thus a mechanism is provided, not only for the transport of a mercurial through the blood stream, but also for egress from the blood stream in combination with one of these small diffusible thiols. Simple mercurials, such as the methylmercury halides, are 100 times as soluble in lipids as in water. While we have pointed out that the amount of such halide present at any one time must be very small in the presence of excess thiol, the Mass Law states that a definite infinitesimal amount is always present. It also holds that, if any should leave the system by dissolving in a lipid membrane, more would dissociate from the protein-mercurial complex to maintain the equilibrium so that eventually all of the mercurial could diffuse through the membrane. Such phenomena must explain the ready diffusibility of methylmercury halides, since they rapidly distribute to all tissues of the body, recognizing no barriers (TABLE 3). In contrast, as others will point out in this symposium, other larger mercurials may exhibit highly selective regions of localization. These mercurials do not appear to be selectively soluble in lipid solvents; furthermore, they seem to be of such large size as not to diffuse readily through the pores in cell membranes. The upper limit of size for ready diffusion of hydrophylic substances is not yet well known; however, even glucose, an uncharged molecule, appears to enter cells only by active transport; in the case of charged molecules, even smaller molecules may be excluded.

The bivalency of inorganic mercury, despite its small size, may act to restrict further its diffusibility since, with both bonds clinging to the protein, the amount of time when it is free for diffusion must be reduced still further. This bivalency may also explain its ability to coagulate proteins since, by binding to adjacent protein molecules, it can link them together, causing aggregation.

Finally, the pharmacological behavior of metallic mercury appears comprehensible in the terms of its lipid solubility, which permits universal distribution followed by oxidation to reactive mercuric salts. The solubility of mercury at 40° C. has been estimated to be 2.7 mg./l. in pentane, 0.6 mg./l. in methanol,[5] and 0.02 mg./l. in water.* The solubility in body lipids is probably intermediate between that in pentane and methanol. The mercury content of saturated air is only 60 μg./l. at 40° C.; therefore the partition coefficient between air and lipid would be approximately 20 in favor of the lipid. These data may explain the almost quantitative removal of mercury vapor from respired air as reported by Shepherd and Schuhmann.[7]

However, Stock,[6] has shown that mercury dissolved in water oxidizes rapidly. Thus, while the solubility of mercury in air-free water is only 0.02 mg./l., in the presence of air, this solubility increases at the rate of 1 mg./l. per day until the saturation value for mercuric oxide is reached. In solutions containing chloride the solubility rapidly increases to the saturation value for mercurous chloride.

Stock[6] showed that blood absorbed mercury from air rapidly and completely. However, he did not determine the state of mercury in blood. I assume it exists transiently as the metal dissolved in blood lipids. I assume that, following its transport in this form to sensitive tissues such as the brain, it is oxidized and thus fixed within cells. The same permeability barriers that prevented the ingress of mercuric salts would now prevent their egress, and the mercury would accumulate, producing chronic effects. Such accumulation is shown in TABLE 3. Similar considerations of lipid solubility and subsequent reactivity would seem applicable to the extremely toxic dialkyl mercurials.

In TABLE 3 I have assembled data on the mercury distribution in humans following exposure to various forms of mercury in both toxic and subtoxic amounts. The two fatalities reported by Ahlmark[11] and by Lundgren and Swennson,[12] followed prolonged exposure to methylmercury and ethylmercury salts both through the vapor and through skin contact. The data on distribution of mercaptomerin were obtained with radioactive mercury on terminal patients. The cases described by Lomholt[14] and by Sollmann and Schreiber[15] died from overdoses of mercuric salts taken by mouth or absorbed from inunctions. Brigatti's cases,[16] while all showing symptoms of chronic mercurialism, presumably died of unrelated causes. The following generalizations can be made about these data:

---

* Stock reported the solubility of mercury in water at 88° C. to be 0.3 mg./l. With the aid of vapor pressure data I have extrapolated this value 0.02 mg./l. at 40° C. Stock measured the solubility at 30° C. as 0.02 mg./l. However this value may be too high due to oxidation by traces of oxygen.

Methylmercury, it will be noted, is quite uniformly distributed throughout the body. This might be anticipated from its favorable distribution in the lipids, as already pointed out in the discussion. The other compounds show unique patterns of distribution.

The mercaptomerin content of all organs except the kidney appears closely related to, if not completely predicated on, their content of blood plasma, suggesting that this diuretic does not enter cells except under special conditions, as in the kidney tubule. This presumably occurs as active absorption from glomerular filtrate of the mercurial that has been carried there in combination with a small mercaptan. The fact that the mercurial was administered as a mercaptide complex (mercaptomerin) does not mean that a special distribution will ensue. I have pointed out that all mercurials must be rapidly converted to mercaptides *in vivo*. Furthermore, Weiner and Müller[8] have shown that Salyrgan is excreted as a thiol complex. However, this does not mean that the mercaptide form of the mercurial does not possess special properties affecting its administration. It would seem, in general, to be a very desirable type of preparation. Mercurials given as their hydroxides, chlorides, or inner salts must show a strong avidity for a large number of groupings on proteins, thus producing extreme local irritation by crowding onto a few molecules* and delaying distribution of the mercurial among the available thiols throughout the body.

Mercuric salts are characterized by very low blood levels and by high preferential concentrations in kidney, liver, and spleen. Their distribution therefore appears to involve transport by serum albumin to cell surfaces followed by exchange to proteins of even higher avidity within the cell. This hypothesis takes into account the permeability of liver capillaries and the filtration mechanism of the kidney.

Finally, the tendency to concentrate appreciably in nervous tissue is a characteristic of metallic mercury.† This may be due to transport as the free metal dissolves in lipids, as already discussed. The concentrations elsewhere appear strongly to resemble mercuric salts. However, the meager data presented might also be interpreted as indicating that prolonged exposure is a prerequisite for its significant accretion in the nervous system. In this connection, it might be well to point out that the neuropsychiatric syndromes are also slow to develop even with the lipid-soluble organic mercurials. The appearance of these syndromes is accompanied by marked histological changes of a degenerative nature; this indicates that the mercurial does not directly inhibit nervous function but, rather, blocks the neurons' metabolism, producing necrosis and irreversible damage.

The limited analytical data on the distribution of mercury in human tissues indicate that pathological effects are the result of real concentrations of mercury in the affected organ. In the case of the brain, which has been considered extremely sensitive to mercury,[9] mental impairment has been found at levels of greater than 1 part per million. In view of the prolonged administration of mercurials today and of the known tendency of some forms of mercury to accumulate, it would seem desirable to collect additional data on the mercury content of all human tissues* following prolonged administration. Comparative data on otherwise equally acceptable mercurials might then furnish a basis for preference.

---

* See footnote (†), p. 455.

† Brigatti[17] also found high brain levels in rabbits that had breathed mercury vapor under controlled conditions until death (25 to 40 days). A one hundredfold variation in the mercury level was observed from animal to animal. Similar variations were found in other tissues.

In conclusion, I have shown that some general principles exist for predicting the pharmacological behavior of mercurials and that mercaptide formation is a fundamental concept. Nevertheless, sulfhydryl groups occur so widely in proteins and with such varying affinities for mercury that the pharmacologically active sites are not yet known.

Acknowledgment

I am particularly indebted to William Wolins, also of the Brookhaven National Laboratory, for his constructive criticism, which has provided the medical background for this paper.

References

1. Weissman, N., E. B. Schoenbach, & E. B. Armistead. 1950. J. Biol. Chem. **187:** 153
2. Hughes, W. L. 1950. Cold Spring Harbor Symposium. **14:** 79–84.
3. Grupe, W. Unpublished data.
4. Racher, E. 1954. *In* Glutathione, a Symposium. Academic Press. New York, N. Y.
5. Reichardt, H. & K. F. Bonhoeffer. 1931. Z. Physik. **67:** 780.
6. Stock, A. 1934. Z. anorg. Chem. **217:** 241–253.
7. Shepherd, M. & S. Schuhmann. 1941. J. Research Natl. Bur. Standards. **26:** 357.
8. Weiner, I. M. & O. H. Müller. 1955. J. Pharmacol. Exptl. Therap. **113:** 241–249.
9. Stock, A. 1942. Ber. deut. chem. Ges. **75:** 1530–1535.
10. Stock, A. 1940. Z. Biochem. **304:** 73.
11. Ahlmark, A. 1948. Brit. J. Ind. Med. **5:** 117.
12. Lundgren, K. & A. Swennson. 1949. J. Ind. Hyg. Toxicol. **31:** 190.
13. Aikawa, J. K. & R. Fitz. 1956. J. Clin. Invest. **35:** 775–778.
14. Lomholt, S. *In* Sollmann & Schreiber (see reference No. 15).
15. Sollmann, T. & N. E. Schreiber. 1936. Arch. Internal Med. **57:** 46.
16. Brigatti, L. 1949. Med. lavoro. **40:** 233.
17. Brigatti, L. 1949. Med. lavoro. **40:** 240.

---

* Stock[10] has observed a large concentration of mercury in the pituitary in "normals."

RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND BIOLOGICAL ACTIVITY IN MERCURIAL COMPOUNDS*

By Harris L. Friedman
Lakeside Laboratories, Milwaukee, Wis.

Mercury, either as the finely divided metal or its salts, has a pronounced effect on living organisms. This paper reviews the more important therapeutic uses of mercurials and discusses structure-activity relationships in one restricted series, the organomercurial diuretics.

The medicinal use of mercurials began in the 16th century with the use of calomel as a diuretic. This use was forgotten and rediscovered several times[1] until it was re-established in therapy by Jendrassik in 1885.[2] Since the acceptance of the germ theory of disease, mercury salts have played a role as antiseptics and disinfectants. Bichloride, for example, has been used since the time of Koch.

Some of the therapeutic uses of elemental mercury and its inorganic salts are as follows:

Antiseptic ointments:
- Colloidal Hg
- $HgNH_2Cl$

Cathartics:
- Hg (blue mass)
- HgCl (calomel)

Diuretics:
- HgCl (calomel)

Germicides:
- $HgCl_2$
- $Hg(CN)_2$
- HgI_2

Antisyphilitics:
- Colloidal Hg
- HgS
- HgO

Except for topical use (ammoniated mercury ointment) and as a disinfectant ($HgCl_2$), these compounds are seldom, if at all, employed in modern therapy.

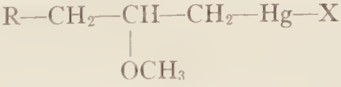
Following the discovery of the organomercurials in the latter half of the 19th century, many of these compounds were introduced as therapeutic agents, but only a few have stood the test of time. The following are some of the compounds that have been used in the past or are used today:

Fungicides, germicides:
- Ethyl mercury Et—Hg—X
- Phenyl mercury ϕ—Hg—X
- Pyridyl mercury Py—Hg—X

Topical germicides:
- Merbromin (Mercurochrome)
- Mercocresols (Mercresin)
- Nitromersal (Metaphen)
- Thimerosol (Merthiolate)

Antisyphilitics:
- Hg salicylate
- Asurol
- Novasurol

Diuretics:



$$R-CH_2-\underset{\underset{OCH_3}{|}}{CH}-CH_2-Hg-X$$

Of these, ethyl and phenyl mercuric salts are currently used as fungicides and germicides. The topical germicides are still popular, although they are losing ground to other classes of compounds. Mercurials are no longer used in the treatment of syphilis.

---

* Some of the data included in this paper were presented at the meeting of the American Chemical Society in April 1955, in Cincinnati, Ohio.

Today the organomercurials find their most important medical use as diuretics. This paper is concerned with these compounds because they offer excellent illustrations of the problems involved in the determination of biological activities and the correlation of biological activity with chemical structure. It has often been emphasized that no correlation need exist between chemical structure and certain types of biological activity; structurally nonspecific agents, such as the narcotics, are well known.[3] The synthetic chemist, however, needs some guide to follow in the search for improved therapeutic agents. The desired relationship may be masked by a wrong test, by faulty technique, or by the misuse of structural formulas, but a relationship revealed, even if valid only for a restricted series, is of inestimable value.

BIOLOGICAL COMPARISONS

The biological potencies of completely different types of compounds can be compared if dose-response curves are plotted and comparisons made at equal dosages, provided that the curves are approximately parallel. The data will be more useful if the compounds can be compared similarly with a selected standard. For valid structure-activity comparisons, certain restrictions must be imposed: the drugs being compared must act by the same mechanism and the structures under comparison must be those responsible for the biological activities being compared. Obviously these facts cannot always be known; an observed phenomenon may be produced by various mechanisms, and many compounds are merely the precursors of the active forms. It is essential that structure-activity correlations be not the results of wishful thinking or self-delusion.

Of the hundreds of mercurials presumably prepared for study as diuretics, the potencies of only a small number have been recorded in the literature. Only a few of the latter have been the subjects of proper biological comparison.

Many species of animals have been used for diuretic assay—cats, dogs, mice, rats, rabbits, and guinea pigs. Both hydrated and normal animals have been employed. Diuretic potency has been expressed in terms of the excretion of water, chloride, sodium, or even mercury. This makes it difficult to compare the results reported by one author with those achieved by another. Toxicity comparisons, as will be seen later, are even more difficult because of the multiple effects produced by mercurials at different dose levels and on administration for different lengths of time. Edematous humans, the most desirable subjects for comparison, are discussed elsewhere in this monograph. In this paper, the term "diuretic potency" will refer, in practically all instances, to urinary output in normal dogs after the parenteral administration of organomercurials. Potency comparisons have been made with a selected standard, meralluride U.S.P. (Mercuhydrin).

Inorganic Mercurials

Inorganic mercurials are no longer used in therapy because they are too toxic and too unreliable in diuretic action, but their historic role requires brief mention. The following types have been used: colloidal Hg; HgCl (calomel); $HgCl_2$ (bichloride); $HgBr_2$; $Hg(CN)_2$; $Hg(OCN)_2$; salts of organic acids (for example, Hg benzoate); and salts of organic nitrogen compounds (for example, Hg succinimide). Fourneau and Melville,[4] using rabbits, and Sollmann and his co-workers,[5] using humans, have shown that diuretic potency varied, and that $HgCl_2$, $HgBr_2$, and $Hg(OCN)_2$ were the most potent of the compounds tested. Comparison of their data with those from the organomercurials available at the time demonstrated that the inorganic compounds were several times more potent. However, organomercurials of much greater diuretic potency are now available, and in our laboratories we have encountered many organomercurials more potent than the inorganic compounds when compared in terms of dose of mercury per kilogram of body weight. Sollmann, who compared the compounds in terms of mercury excretion, stated that the inorganic compounds were several thousandfold more potent than the organomercurials; he did not, however, compare dose-responses.

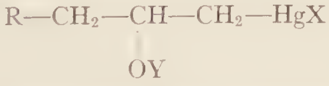
Organomercurials

Blumenthal and Oppenheim[6] had noted in 1913 that a wide variety of organomercurials produced diuresis in rabbits, but their observation stimulated no further study. It was Vogl's[7] observation of diuresis during treatment of a syphilitic patient with Novasurol, and pursuit of this clue by Saxl and Heilig,[8] that led to the development of the modern organomercurial diuretics.

Organomercurials constitute a potentially limitless class, but most of the compounds thus far studied fall into limited categories because of availability of intermediates or ease of preparation.

Novasurol, which is of the general type Aryl—Hg—X, was replaced by other compounds although, diuretically, it is as potent as the standard; it was abandoned because of its toxicity. For reasons either of weak diuretic potency or excessive toxicity no compound of the general classes R—Hg—R or R—Hg—X, where *R* is aliphatic, aromatic, or heterocyclic, has become clinically useful.

All the presently used organomercurials are of the general type



$$R—CH_2—\underset{\displaystyle OY}{\underset{|}{CH}}—CH_2—HgX$$

that is, mercurated allyl derivatives. For comparisons of structure-diuretic potency it is convenient first to discuss the effects of the *Y* and *X* groups, inasmuch as these can be varied independently of group *R*.

The nature of group *Y* is dependent upon the solvent used in the mercuration reaction; if the solvent is water, *Y* is hydrogen; if an alcohol, *Y* may be a lower alkyl, hydroxyalkyl, or alkoxyalkyl group. Most mercurations are run in methyl alcohol or (less frequently) in water, and it is noteworthy that in the literature no distinction with respect to diuretic potency is made between compounds prepared in these solvents. From the published data, such as those of Halpern, Jones, and Gross,[9] and from our own unpublished data the following general conclusion may be drawn: diuretic potency in animals diminishes slightly with increase in the size of the *Y* group, but the difference between the extremes is probably no more than ±25 per cent.

The effect of group *X* on diuretic potency is more pronounced. The products of the mercuration reaction contain *X* either as acetoxy or hydroxy, and the two are indistinguishable in diuretic potency. When *X* is theophylline, the effect on diuretic potency is controversial: some workers state that replacement of —OH or —OAc by theophylline produces a marked increase[10] in diuretic potency, whereas others have found no change[11] or, perhaps, only a slight increase.[12] It is conceivable that the parent compound or the species of animal used in the diuretic test may account for these differences. Results obtained in our own laboratories, using dogs, have shown that whether *X* is hydroxy, acetoxy, chloride, theophylline, or thioglycolic acid, the diuretic potency remains unchanged.

Some thiol-containing compounds will abolish diuresis completely, but in an unpredictable manner. For example, the combination of 1 mol BAL (dimercaptopropanol) with 2 mol Mercurin abolishes diuretic activity, but leaves unaffected the potency of the compound formed with 2 mol mersalyl.[13]

Thus, in comparing the diuretic potency of the organomercurials derived from allyl compounds, the groupings *X* and *Y* may be ignored except in certain unusual cases.

A selected group of those types of organomercurials most studied follows:

Aryl- or heteroyl-allyl. Representative members of this type are shown in FIGURE 1. Diuretic potency varies from almost inactive (allyl on carbon of a

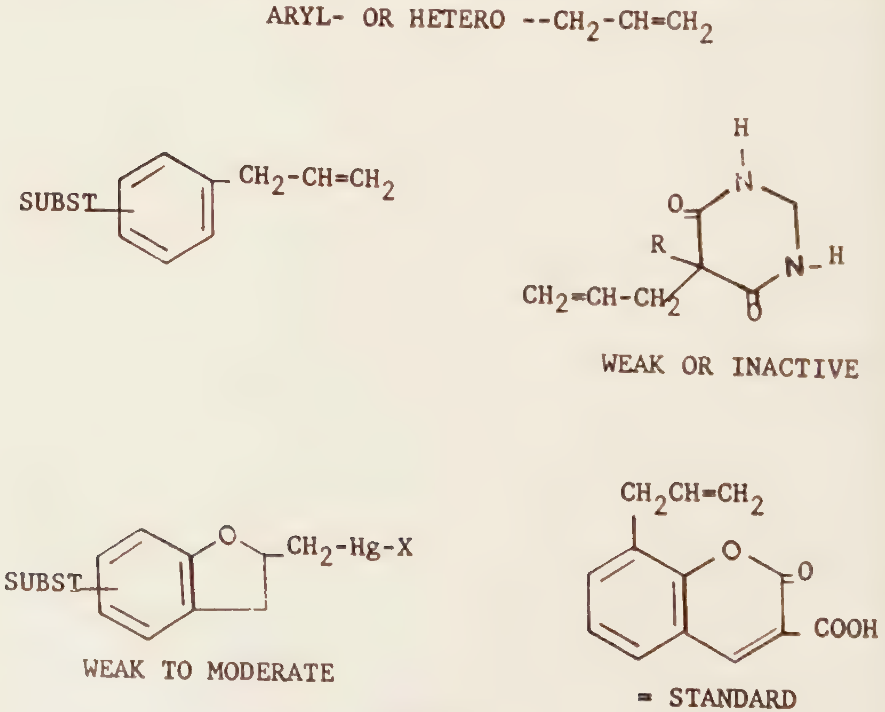


Figure 1

pyrimidine ring) to equal that of the standard. The mercurated *o*-allylphenols are interesting in that the compounds resulting from ring closure (benzodihydrofurans) are stable to strong acid, in contrast to most mercurated allyl compounds;[14] their diuretic potency is generally less than that of the standard. The allylcoumarin is the parent substance of the clinically used mercumatilin.

Allyl alcohol and its derivatives. Mercurated allyl alcohol and its simple derivatives (FIGURE 2) possess little, if any, diuretic activity.[15] The ethers and esters of mercurated allyl alcohol are also generally weak. An exception is the mercuration product of 3-allyl mannitol, which is approximately twice as potent as the standard.[16]

Allylamines. Mercurated arylalkylamines, shown in FIGURE 2, are active. Those nitrogen-containing heterocyclic compounds that possess an allyl group on a ring nitrogen also give diuretically active mercurated derivatives, similar in activity to the standard, and much more active than those previously mentioned where the allyl group was attached to a carbon[17] in a heterocyclic ring.

Allylamides. This group (FIGURE 3) has been fruitful and comprises a large proportion of the published compounds. All the major classes of organic compounds are represented therein. Several of the diuretics used clinically are of this type: mercurophylline, mersalyl, merethoxylline, and mercaptomerin. These are of approximately the same potency, equal to or slightly less than

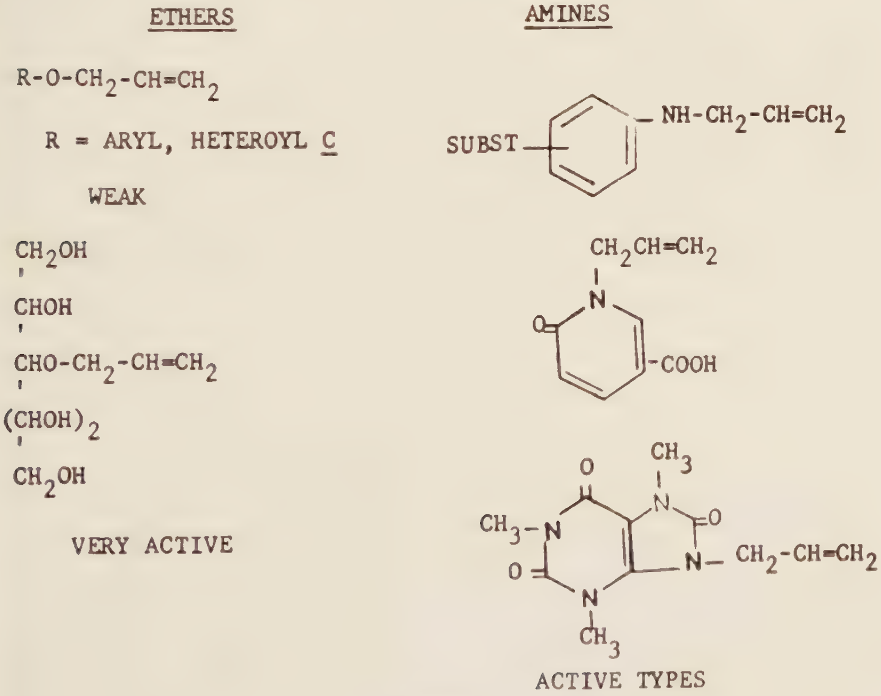


FIGURE 2

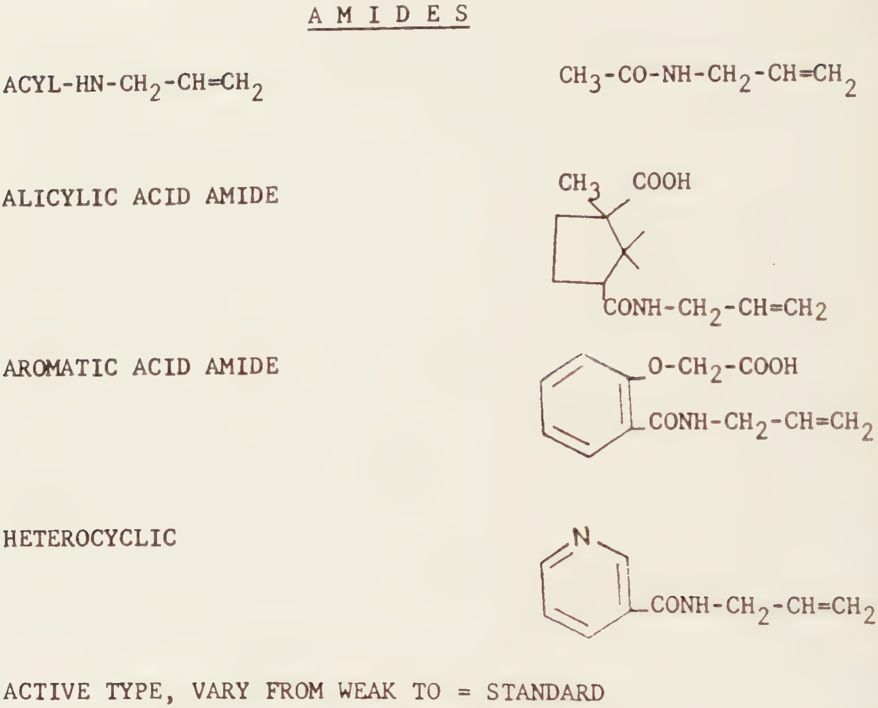
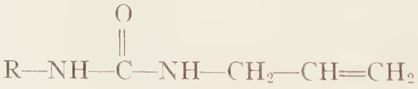


FIGURE 3

that of the standard. Mercurated allylamides of the lower fatty acids are generally less potent than the standard.[18]

Allylureas. The following types of compounds have been tested



$$R{-}NH{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH{-}CH_2{-}CH{=}CH_2$$

R = succinoyl (standard)

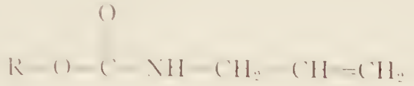
R = H. Very active.

R = alkyl, aryl. Moderate to weak.

Methyl homolog (methallyl). Very active.

This has also been a fruitful group and contains 2 compounds that are used clinically: meralluride, the standard we have been using for comparison; and chlormerodrin. On varying group *R*, activity varies from approximately 4 times the standard (*R* = H) to quite weak (*R* = phenyl).[19a, 19b] Generally, diuretic potency decreases with increase in size of group *R*, but not always. The methallyl analog is the most potent of the series (greater than 5 times the standard) but is proportionately increased in toxicity.

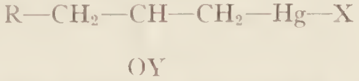
Urethanes. Mercurated urethanes, of the type shown below, are of the same diuretic potency as the standard.[20]



$$R-O-\overset{\displaystyle O}{\overset{\|}{C}}-NH-CH_2-CH=CH_2$$

Toxicity. Low toxicity is of primary importance if an agent is to be useful in the treatment of a chronic disease. It is not difficult to synthesize compounds of sufficient diuretic potency, but most compounds have failed to be clinically useful because of excessive toxicity. Toxicity, of course, depends on dose, route of administration, length of administration, species, and so on. If high doses of organomercurials administered intravenously to animals are given too rapidly, death from cardiac standstill and/or respiratory failure (hyperacute toxicity) can be produced in a few hours. One can select smaller doses that are not immediately fatal, but will produce death in 7 to 14 days (acute toxicity). Lower, sublethal doses can be given for months in order to study chronic toxicity. In addition, local tolerance to intramuscular or subcutaneous injection may be considered. Finally, as with all compounds, allergic manifestations may be seen, but these probably depend as much on the recipient as on the compound.

In contrast to most types of compounds, it is possible to modify certain toxicity characteristics of the organomercurials without altering their diuretic potency. One cannot always predict to what extent such alterations can be made, but certain factors have been elucidated and are worthy of summary. If we consider mercurated allyl compounds of the type



$$R-CH_2-\underset{\displaystyle OY}{CH}-CH_2-Hg-X$$

the following generalizations concerning the effects of the groups *R*, *Y* and *X* on toxicity can be made: all types of toxicity are primarily determined by group *R*, but for any given *R* group certain types of toxicity can be modified by variation of group *X*. The *Y* group has a negligible effect on any type of toxicity.

The compounds formed directly from the mercuration reaction, that is, those in which *X* is —OH or —OAc, generally possess the highest cardiac toxicity (hyperacute toxicity) and produce the greatest local tissue irritation of all *X* groups. By replacing these *X* groups with a theophylline[21] or thioglycolic acid residue,[22a, 22b] local irritation and cardiac toxicity may be markedly reduced. Acute (14-day) and chronic toxicity are little affected by theophylline. Thioglycolic acid may, however, have either no effect on acute and chronic toxicity[23] or an adverse effect.[24a, 24b] It can thus be seen that replacement by a particular group does not always produce the same effect, and that the effect on toxicity may be desirable or the opposite. There is, therefore, no true structural correlation. Not all thiol-containing *X* groups are equally effective in decreasing cardiac toxicity or local irritation: a gradation from highly effective to ineffective has been observed.[25] Similarly, theophylline does not diminish cardiac toxicity for all *R* groups, but only for certain compounds, and in unpredictable manner.[26] Nonetheless, it is often possible to modify favorably the toxicity of an organomercurial compound, and it is sometimes worthwhile to attempt such a modification.

Physical properties. Correlation of diuretic potency with a readily measurable physical property is obviously highly desirable. As yet no successful attempt in this area has been recorded.

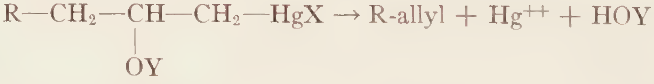
In 1939 Breyer[27] divided organomercurials into 2 main categories. He considered those readily soluble in water as diuretic, those insoluble in water, but lipid-soluble, as poor diuretics, although effective as antiluetics.

Fourneau and Melville[4] noted that, in 3 isomeric organomercurials, "diuretic potency was in direct relation to the facility in dissolving the substances by weak alkalis." Results found in our own laboratories do not demonstrate any correlation between diuretic potency and ease of solution in alkali.

Many authors have discussed the role of ionization in relation to diuresis, local irritation, or systemic toxicity.[28] In many cases, however, what the author had in mind was not ionization but decomposition to inorganic ("ionizable") mercury. In other instances ionizability has been confused with reactivity or firmness of combination with nitrogen- or sulfur-containing compounds. In our laboratories Rowland[29] measured the ionization of many organomercurials

$$R{-}Hg{-}X \rightleftharpoons R{-}Hg^{+} + X^{-}$$

but found no correlation with diuretic potency or with acute (14-day) toxicity. We ourselves have found no correlation between decomposition with mineral acid



$$R{-}CH_2{-}\underset{\displaystyle OY}{\underset{|}{CH}}{-}CH_2{-}HgX \rightarrow R\text{-allyl} + Hg^{++} + HOY$$

and either diuresis or toxicity.

Lehman[30] has stated that "reactivity" of the second valence bond of the mercury in an organomercurial is a factor in tissue irritation and cardiac toxicity. This is more plausible than an assumption that local irritation can be correlated with ease of ionization. Indeed, it should be possible to find an *in vitro* test for relative binding strength that would correlate with tissue tolerance.

CONCLUSIONS

At present it is not possible to examine a chemical structure and predict its biological activity, although, if the compound is related to already known types, a good guess can often be made. In a restricted series, where some compounds have been studied, predictability is on a firmer basis. Thus, as a generality, it can be predicted that a mercurated allyl compound will possess some diuretic activity.

For years it had been assumed that, since mercury is the component common to all the organomercurials, diuresis must result from breakdown into small amounts of active inorganic mercury. The recent studies of Müller,[31] of Handley,[32] and of Pitts[33] have shown that the intact organomercurial is diuretically active. Thus the foundation has been laid for a better understanding of the role of structure in relation to diuresis and toxicity. Much remains to be accomplished and it is anticipated that rapid progress will be made in the near future.

References

1. Philip, A. P. W. 1834. On the Influence of Minute Doses of Mercury. Henry Renshaw. London, England.
2. Jendrassik, E. 1885. Calomel as a diuretic. Deut. Arch. klin. Med. **38:** 499.
3. Albert, A. 1951. Selective Toxicity. : 28. John Wiley & Sons. New York, N. Y.
4. Fourneau, E. & K. I. Melville. 1931. Studies in mercurial chemotherapy. II. The quantitative evaluation of mercurial diuresis and its relation to chemical constitution. J. Pharmacol. Exptl. Therap. **41:** 47.
5. Sollmann, T., N. E. Schreiber & H. N. Cole. 1936. Comparative diuretic response to clinical injections of various mercurials. Arch. Internal Med. **58:** 1067.
6. Blumenthal, F. & K. Oppenheim. 1913. Aromatic mercury compounds. IV. Biochem. Z. **57:** 261.
7. Vogl, A. 1950. The discovery of the organic mercurial diuretics. Am. Heart J. **39:** 881.
8. Saxl, P. and R. Heilig. 1920. The diuretic activity of Novasurol and other mercurial injections. Wien. klin. Wochschr. **33:** 943.
9. Halpern, A., J. W. Jones & E. G. Gross. 1948. The synthesis and study of some mercurated N-allylbarbital derivatives. J. Am. Pharm. Assoc. Sci. Ed. **37:** 333.
10. von Issekutz, B. & F. von Vegh. 1928. The diuretic activity of organic mercury compounds. Arch. exptl. Pathol. Pharmakol. **138:** 245.
11. Pontius, J. R., L. A. Crandall & L. E. Hines. 1936. Diuretic properties of organic mercurial compounds. J. Am. Med. Assoc. **106:** 416.
12. Roby, C. C. & C. Pfeiffer. 1942. Relative increase in chloride excretion in the dog after graduated doses of mercurial diuretics. Am. J. Physiol. **135:** 591.
13. Short, E. I. 1952. Combination of mercurial diuretics with dimercaprol. J. Pharm. Pharmacol. **4:** 985.
14. Adams, R., F. L. Roman & W. N. Sperry. 1922. The structure of the compounds produced from olefins and mercury salts: mercurated dihydrobenzofurans. J. Am. Chem. Soc. **44:** 1781.
15. Wiese, G. A. & J. W. Jones. 1950. The synthesis of mercurated 8-allyloxy-caffeine and mercurated 1,3,7-trimethyl-9-allyluric acid, a study of their toxicity and diuretic activity. J. Am. Pharm. Assoc. Sci. Ed. **39:** 286. See also reference No. 10.
16. Moyer, J. H., R. G. McConn, R. A. Seibert, E. W. Dennis & W. Hughes. 1955. A comparative study of Mersoben, Mercuhydrin, Neohydrin, and Diamox. J. Chronic Diseases. **2:** 670.
17. Cahen, R. L. 1947. On the potency and toxicity of a new mercurial diuretic. J. Am. Pharm. Assoc. Sci. Ed. **36:** 139. See also references Nos. 9 and 15.
18. Rowland, R. L., W. L. Perry & S. Gerstein. 1951. Mercurial Diuretics. II. Methoxymercuration of N-allylamides. J. Am. Chem. Soc. **73:** 91.

19a. Rowland, R. L., W. L. Perry, E. L. Foreman & H. L. Friedman. 1950. Mercurial Diuretics. I. Addition of mercuric acetate to allylurea. J. Am. Chem. Soc. **72:** 3595.

19b. Rowland, R. L., W. L. Perry & S. Gerstein. 1951. Mercurial diuretics. IV. Methoxymercuration of substituted allylureas. J. Am. Chem. Soc. **73:** 3691.

20. Miescher, K. & K. Hoffmann. 1939. Acyloxy mercury urethanes. U. S. Pat. 2,156,598.
21. DeGraff, A. C. & R. C. Batterman. 1935. Reaction at site of injection of mercurial diuretics as influenced by theophylline. Proc. Soc. Exptl. Biol. Med. **32:** 1546.

22a. Lehman, R. A. 1947. Further study on the acute toxicity of mercurial diuretics. Proc. Soc. Exptl. Biol. Med. **64:** 428.

22b. Lehman, R. A., H. Taube & E. E. King. 1949. A comparative study of the local toxic action of mercurial diuretics. Proc. Soc. Exptl. Biol. Med. **71:** 1.

23. Handley, C. A., J. H. Moyer & J. R. Thomas. 1953. The effects from prolonged administration of the mercurial derivatives of 2-methoxypropylurea in dogs. J. Pharmacol. Exptl. Therap. **108:** 424.

24a. Capps, R. T., F. L. Kozelka & O. S. Orth. 1950. Chronic toxicity of Thiomerin compared to other mercurial diuretics. Proc. Soc. Exptl. Biol. Med. **74:** 511.

24b. BARRETT, M. J. 1950. Chronic acute effects of Mercuhydrin and Thiomerin on renal tubular function in the dog. J. Pharmacol. Exptl. Therap. **100:** 502.
25. WERNER, L. H. & C. R. SCHOLZ. 1951. Mercurial diuretics and their detoxification by thiols. 12th Intern. Congr. Pure & Appl. Chem. Abs. : 341. New York, N. Y.
26. DEGRAFF, A. C. & R. A. LEHMAN. 1952. The acute toxicity of mercurial diuretics. J. Am. Med. Assoc. **119:** 998.
27. BREYER, B. 1939. Effect of substituents on the chemical, physicochemical and biological behavior of chemical compounds. Biochem. Z. **301:** 65.
28. BURGER, A. 1951. Medicinal Chemistry. : 254. Interscience. New York, N. Y.
29. ROWLAND, R. L. 1952. Mercurial Diuretics. VI. Ionization of organic mercurials. J. Am. Chem. Soc. **74:** 5482.
30. LEHMAN, R. A. 1951. Water soluble sulfur-containing organic mercury compounds. U. S. Pat. 2,576,349. See also reference No. 22.
31. WEINER, I. M. & O. H. MÜLLER. 1955. Polarographic studies of mersalyl-thiol complexes and of the excreted products of mersalyl. J. Pharmacol. Exptl. Therap. **113:** 241.
32. HANDLEY, C. A. & R. A. SEIBERT. 1956. The urinary excretory products after meralluride administration. J. Pharmacol. Exptl. Therap. **116:** 27.
33. GREIF, R. L. & R. F. PITTS. 1956. Distribution of radiomercury administered as labeled chlormerodrin in the kidneys of rats and dogs. J. Clin. Invest. **35:** 38.

DISCUSSION: PART I

Frank C. Collins, *Chairman*
Polytechnic Institute of Brooklyn, Brooklyn, N. Y.

Question: Is there a reversible nickel-amalgam electrode that is properly sensitive to nickel content?

Cecil V. King (*New York University, New York, N. Y.*): No important cell measurements with nickel amalgams or amalgamated nickel electrodes seem to have been reported.

George F Wright (*University of Toronto, Toronto, Ont., Canada*): Does any metal, except possibly gold, form a reasonably stable amalgam with mercury? We are using a zinc-amalgam base for dielectric-constant work, and it does not last very long.

Edward Wichers (*National Bureau of Standards, Washington, D. C.*): Silver will also form a stable amalgam with mercury.

Question: How long must you watch for scum formation to be sure that mercury is contaminated?

Edward Wichers: It is usually a matter of a few hours, depending on the nature and concentration of the base metal contaminant. In the demonstration that I prepared, contamination with 5 parts of zinc per million gives a spectacular effect in an hour or two.

George F Wright: I believe that a little-known reaction reported in the Russian literature[1] might make it possible to obtain some of the quaternary ammonium mercurials suggested by Hughes.

Reference

1. Friedlina, R. K. & N. S. Kochetkova. 1945. Bull. Acad. Sci. URSS Classe sci. chim. : 128.

W. L. Hughes, Jr. (*Brookhaven National Laboratory, Upton, N. Y.*): I might point out why I should like to have mercurials of this nature. In enzymes, the essential thiols must be surrounded by other groups of unknown nature. A study of the interactions of several mercurials with such an enzyme should show variations interpretable in terms of the interaction of the accessory groupings on the mercurial with neighboring groups on the enzyme. Probably the simplest variations to interpret would be those due to an alteration of charge in the mercurial as in the series

$$^{-}O_3SCH_2Hg^{-},\ CH_3Hg^{-},\ (CH_3)_3N^{+}CH_2Hg^{-}$$

Question: Are there other good techniques for titrating mercurials?

W. L. Hughes: Ingram[1] has shown that mercurials will stoichiometrically inhibit silver binding by thiols as observed in amperometric titration. I suggest that this observation could be used in reverse for titrating mercurials with thiols in the presence of a trace of silver ions. The disappearance of the silver ion diffusion current would serve as an end point. Probably cyanide could be used in place of a thiol for this titration.

Reference

1. Ingram, V. M. 1955. Sulphydryl groups in haemoglobins. Biochem. J. (London). **59:** 653.

Question: Have you measured the association constant of unreactive sulfhydryls; for example, in ovalbumin?

W. L. Hughes: No, it is very hard to obtain equilibrium measurements under these conditions. The reaction is so slow that denaturation may interfere.

Robert A. Lehman (*Campbell Pharmaceutical Company, New York, N. Y.*): I question the measurement of the extent of ionization of mercurials mentioned by Friedman. After injection into the body, the mercurial diuretic probably travels as a thiol complex. Moreover, there is very likely an exchange between the circulating thiol complex and, perhaps, an essential thiol enzyme in the kidney. The question of ionization might then be academic.

Harris L. Friedman (*Lakeside Laboratories, Milkaukee, Wis.*): Undoubtedly the combinability (or firmness of combination) of the organomercury compound with a thiol group is far more important than ionization. There are statements in the literature to the effect that the more ionized the compound is, the more potent or the more toxic it is. We were curious to see if this could be substantiated. The study I mentioned was published by Rowland[1] of Lakeside Laboratories and showed no correlation between ionization constant and either diuresis or toxicity.

Reference

1. Rowland, R. L. 1952. Mercurial diuretics. VI. Ionization of organic mercurials. J. Am. Chem. Soc. **74:** 5482–5484.

George F Wright: I, too, have wondered whether degree of ionization is really measured in these cases. I am not satisfied that any proof has been established.

Harris L. Friedman: I agree that organomercurials may not undergo simple ionization. Rowland did not profess to be absolutely certain that he was measuring ionization. He applied the classical procedures and obtained a classical ionization coefficient, whatever that may imply. The paper was submitted for publication with the request that it be reviewed by physical chemists familiar with such measurements. There was no adverse criticism of the paper.

Robert A. Lehman: In the discussion of the inhibition of diuresis by thiol compounds, were the examples given dithiol compounds? Do you know of any case where a monothiol inhibited diuresis?

Harris L. Friedman: The example cited was a dithiol compound. I was referring to the combination of 1 mol BAL (dimercaptopropanol) with 2 mol Mercurin, which is a nondiuretic compound.[1] There is here a one-to-one ratio of Hg-to-SH group. I know of no similar instance in which a monothiol compound was used.

Reference

1. Short, E. I. 1952. Combination of mercurial diuretics with dimercaprol. J. Pharm. and Pharmacol. **4:** 985.

QUESTION: Is it possible to inhibit diuresis temporarily by means of monothiols?

CARROLL HANDLEY (*Baylor University College of Medicine, Houston, Texas*): Cysteine will inhibit diuresis temporarily.

QUESTION: Is ionic mercury ever present in biological fluids?

CARROLL HANDLEY: No, ionic mercury always combines with proteins.

EDWARD WICHERS: King referred to the use of mercury itself as a physic years ago. Is it true that metallic mercury was at an earlier time used as a purgative in case of extreme intestinal stoppage? It seems drastic.

CECIL V. KING: I have read of its administration both to chimpanzees and to humans—with what results I do not know.

ALFRED VOGL (*New York University, New York, N. Y.*): Metallic mercury in large quantities was once used in attempts to overcome intestinal obstruction mechanically by its sheer weight. It is hard to imagine that it ever worked. Nevertheless the procedure was still mentioned in surgical textbooks only two generations ago.

Part II. Pharmacology and Toxicology

TOXIC EFFECTS OF VAPORS OF MERCURY AND OF COMPOUNDS OF MERCURY ON PLANTS

By A. E. Hitchcock and P. W. Zimmerman
Boyce Thompson Institute for Plant Research, Inc., Yonkers, N. Y.

Although the toxicity of mercury vapor to higher plants was known as far back as 1797[1] and was referred to again in 1867,[1] there have been relatively few published reports. The subject was renewed by Zimmerman and Crocker[2] and by Ratsek[3] in 1933 after an accidental injury occurred to greenhouse roses where the soil had been treated with bichloride of mercury ($HgCl_2$). After a lapse of approximately 20 years several cases of accidental injury to roses occurred when paint containing a mercury fungicide was applied to the interior of greenhouses. These accidents were reported by Butterfield[4] and by Dimond and Stoddard.[5] The toxicity of mercury vapor to humans and the precautionary measures recommended were described by Butterfield.[4]

The current generally accepted theory is that the phytotoxicity of mercury compounds is primarily due to the vapor arising from mercury reduced to the metallic state rather than to the vapor of the compound itself.[6] All cases of mercury-vapor toxicity to plants have occurred in a confined atmosphere, and the injury has varied with temperature and other conditions that affect the vaporization of mercury. Similar toxic effects have been caused by emanations after compounds of mercury have been mixed with organic matter, such as soil or paint. All compounds of mercury thus far tested have reacted with organic matter to release elemental mercury. It is the purpose of this report to review the literature and to describe in considerable detail the toxic effect of vapors of mercury and of compounds of mercury in relation to higher plants. We have included unpublished data recently obtained concerning the toxic effect on roses of greenhouse paint containing mercury fungicides.

Effect Reported in 1797 of Mercury Vapor on Plants

The toxic effects of mercury vapor on higher plants were described in 1797 in a letter sent by Lauwerenburgh to Van Mons. Experiments mentioned in the letter were performed by 4 Dutch chemists—Deiman, Paats, Van Troostwyck, and Lauwerenburgh—who showed that when bean, mint (*Mentha crispa*), or *Spiraea salicifolia* were enclosed in bell jars with metallic mercury the leaves were spotted after 1 day's exposure and that, if exposed for several days, the plants died. It was concluded that the toxic emanation from metallic mercury was elemental mercury vapor. Quotations from the above-mentioned letter to Van Mons relating to 7 experiments were published by Boussingault in 1867.[1] Some of these experiments were repeated by Boussingault, who obtained comparable results using mint, petunias, peach twigs, and flax.

Boussingault used a relatively large surface area of mercury (36 cm.^{2}) and in 1 test placed additional mercury (4 cm.^{2} surface area) in the upper part of the bell jar. The temperatures rose from 29° to 31° C. at midday when the bell jars (10 l.) were placed in direct sunlight. The longest period of exposure was 90 hours. Injury to plants was in the form of dark spots and a blackening of the leaves and stems, an eventual collapse of the leaves, so that they hung vertically downward, and a premature falling of leaves the older leaves falling first. Petunia flowers abscissed prematurely, without change in color or texture. The severity of the symptoms increased with the duration of exposure and varied with the species of plants.

The Dutch workers showed that injury to the plants could be prevented by placing a layer of water over the mercury or by coating part of the inside wall of the bell jar with sulfur.[1] These results constituted additional evidence that the toxic emanation from mercury was elemental mercury vapor, although an attempt to obtain mercury-gold amalgamation on a strip of gold suspended in the upper part of the bell jar failed. Boussingault commented that the duration of exposure was probably too short to give a positive test, and he pointed out that the English scientist Michael Faraday had obtained measurable and visible mercury amalgamation with gold after 6 weeks' exposure in darkness and at temperatures below 31° C. In a later report[7] Boussingault described the influence of factors that determined the relative amount of mercury-gold amalgamation that occurred in a closed system. This second report also described tests that furnished an explanation for the counteracting effect of sulfur on mercury vapor, which will be discussed later.

As a final contribution the Dutch workers[1] showed that when a compound of mercury (mercury oxide) was substituted for metallic mercury in the bell-jar tests there was no injury to the plants, but that when the compound was added to the soil of potted mint plants held under a bell jar, it caused the eventual death of the plant. This appears to be the first instance of injury to plants resulting from the addition of a compound of mercury to soil that contains organic matter. An explanation of these results was not given, so that it is not clear whether the Dutch chemists believed the injury to mint in this particular test was caused partly or entirely by vapors arising from reduced mercury.

Further evidence that the Dutch chemists had not considered the reducing action of organic matter in soil on compounds of mercury is contained in a statement to the effect that metallic mercury did not cause injury to plants when it was mixed with soil.[1] This would indicate also that toxic amounts of mercury were not taken up by the plant from soil. Although it was shown many years later that metallic mercury vapor is given off when organic and inorganic compounds of mercury are added to soil,[2, 3, 5, 6] there is no mention in these reports of adding metallic mercury to soil. In the test carried out by the Dutch chemists the mercury perhaps accumulated near the bottom of the pot, where it may have been covered with enough water to prevent the vaporization of a toxic amount of mercury. These same workers had demonstrated that a layer of water over metallic mercury prevented injury to mint.

Two of the experiments carried out by the Dutch chemists were of special interest to Boussingault, who discussed them on p. 925 of the work[1] to which

TABLE 1

SUMMARY OF RESULTS, SHOWING THE EFFECT OF TEMPERATURE, DISTANCE BETWEEN A STRIP OF GOLD (7 cm.^{2}) AND THE SURFACE OF MERCURY, AND THE DURATION OF EXPOSURE ON THE QUANTITY OF MERCURY VAPOR FIXED (AMALGAMATED) BY GOLD*

Distance between mercury and gold (mm.)	Temperature in degrees C.	Time exposed (days)	Increase in weight of gold (mg.)	Color of gold surface	
				Before heating	After heating
10	4–7	60	0	No change	—
10	10–16	60	1–2	No change	—
15	14–20	5	2	No change	—
80	14–20	5	1	No change	—
15	18–28	21	11**	Whitish	Dull all over
80	18–28	21	2**	Dull at base	Dull at base

* Compiled from data in Boussingault's second report.[7]
** Also the amount lost after heating.

reference has already been made. Experiment No. 4 involved the suspension of a piece of gold leaf inside the bell jar containing the mint plant and a container of mercury. In experiment No. 6 the mint was not injured when a portion of the inside wall of the bell jar was coated with sulfur. Dusting the plant with sulfur accomplished the same purpose. The second report published by Boussingault[7] described the influence of several factors on the amount of mercury vapor fixed by a polished strip of gold suspended above mercury in a stoppered test tube. A summary of the compiled results (TABLE 1) shows that the amount of mercury vapor fixed by gold increased with increasing temperature and duration of exposure and with a decreasing distance between the gold and the surface of the mercury. Similar results were obtained with silver. These are the results that would be expected when mercury vaporizes to form elemental mercury vapor in a confined atmosphere. Visible evidence of mercury-vapor fixation by gold occurred only at the higher temperatures (18° to 20° C.), but a measurable increase in the weight of the gold occurred at temperatures of from 10° to 16° C. when the duration of exposure was prolonged to 60 days. The material fixed by gold or silver was not identified as mercury by chemical or spectrographic methods, however, as was done later by other workers.[5, 6]

In attempting to explain the counteracting effect of sulfur on mercury vapor in experiment No. 6, Boussingault carried out tests of his own showing that the counteracting effect occurred in the air. Thus Boussingault not only confirmed the results of the Dutch chemists with respect to the counteracting effect of sulfur, but he explained the protective action of sulfur as due to the formation of mercuric sulfide in the air. His results showed that the same amount (2 mg.) of the bluish-black, irridescent deposit (assumed to be mercuric sulfide) that formed on the suspended gold strip was equal to the amount lost after heating. Furthermore, the heated gold strip regained its original shiny appearance, indicating that there was insufficient free mercury vapor either to produce visible evidence of the amalgamation of mercury with gold or to give a measurable gain in weight.

Efficient and continuous protection of the plant would require a continuous supply of enough sulfur vapor to react with all of the mercury vapor in the air surrounding it. According to Boussingault, the nearly equal densities of sulfur vapor and mercury vapor, given as 6.65 and 6.97, respectively (0° C. and 766 mm.), made this possible. These density values are presumably based upon the density of air as 1.0. This explanation for the protective action of sulfur is of special interest, since an overcoating of lime sulfur paste was recommended 88 years later for preventing the escape of toxic amounts of mercury vapor from greenhouse paint that contained a mercury fungicide.

Accidental and Experimentally Induced Mercury-Vapor Injury

Between 1867 and 1932 no reports relating to the toxic effects of mercury vapor on plants were published. Renewed interest in the subject arose in 1933 when Zimmerman and Crocker[2] reported that, in 1932, Briarcliff roses were accidentally injured throughout an entire commercial rose house in Massachusetts as a result of the application of mercuric chloride ($HgCl_2$) to the soil in a few benches for the purpose of controlling earthworms. Mature flowers appeared faded and lacked the bright pink color characteristic of the Briarcliff variety. A browning of the petals occurred on immature flower buds, and the adjacent part of the peduncle was discolored. Other varieties of roses in the same house did not show the same type of injury.

These results were verified experimentally by tests with Briarcliff, Coolidge, Madame Butterfly, and Templar roses in a rose house at the Boyce Thompson Institute, Yonkers, N. Y. Additional tests made use of potted plants placed in muslin and glass cases. The concentration of $HgCl_2$ solution applied to the soil was 0.025 to 0.2 per cent. The volume of solution applied once or twice to soil in benches was equivalent to that used in a single routine watering of the plants. One quart of the $HgCl_2$ solution was applied to roses grown in 2-gallon jars. Tankage, a fertilizer high in organic matter, was added to some of the bench plots in amounts of 19 oz. to 9 lb. 9.5 oz. per plot, and the highest amount added to the roses in 2-gallon jars was a 6-in. potful. Comparable controls received $HgCl_2$, but no tankage.

Roses in the bench plots eventually developed a flower-bud injury similar to that observed in the commercial rose house (FIGURE 1). The symptoms and the extent of injury were the same on Briarcliff roses in the control plots and in the plots receiving $HgCl_2$. Half-mature flower buds with faded or brown petals failed to open, and they separated easily from the receptacle. The stamens of these buds were dark brown and drier than normal. These symptoms had not previously been mentioned. The other 3 varieties of roses were not badly affected. After 6 weeks an examination of the root systems revealed some retardation of root growth only on plants receiving the higher concentrations of $HgCl_2$ (0.1 and 0.2 per cent). All plants were lifted from the plots, placed in 2-gallon jars, and grown outside. The flowers produced thereafter were normal.

Similar treatments were applied to Briarcliff and Premier Supreme roses grown in 2-gallon jars. After 3 weeks the treated and control plants exhibited the same bud injury as that described for the plot-grown roses. There was as

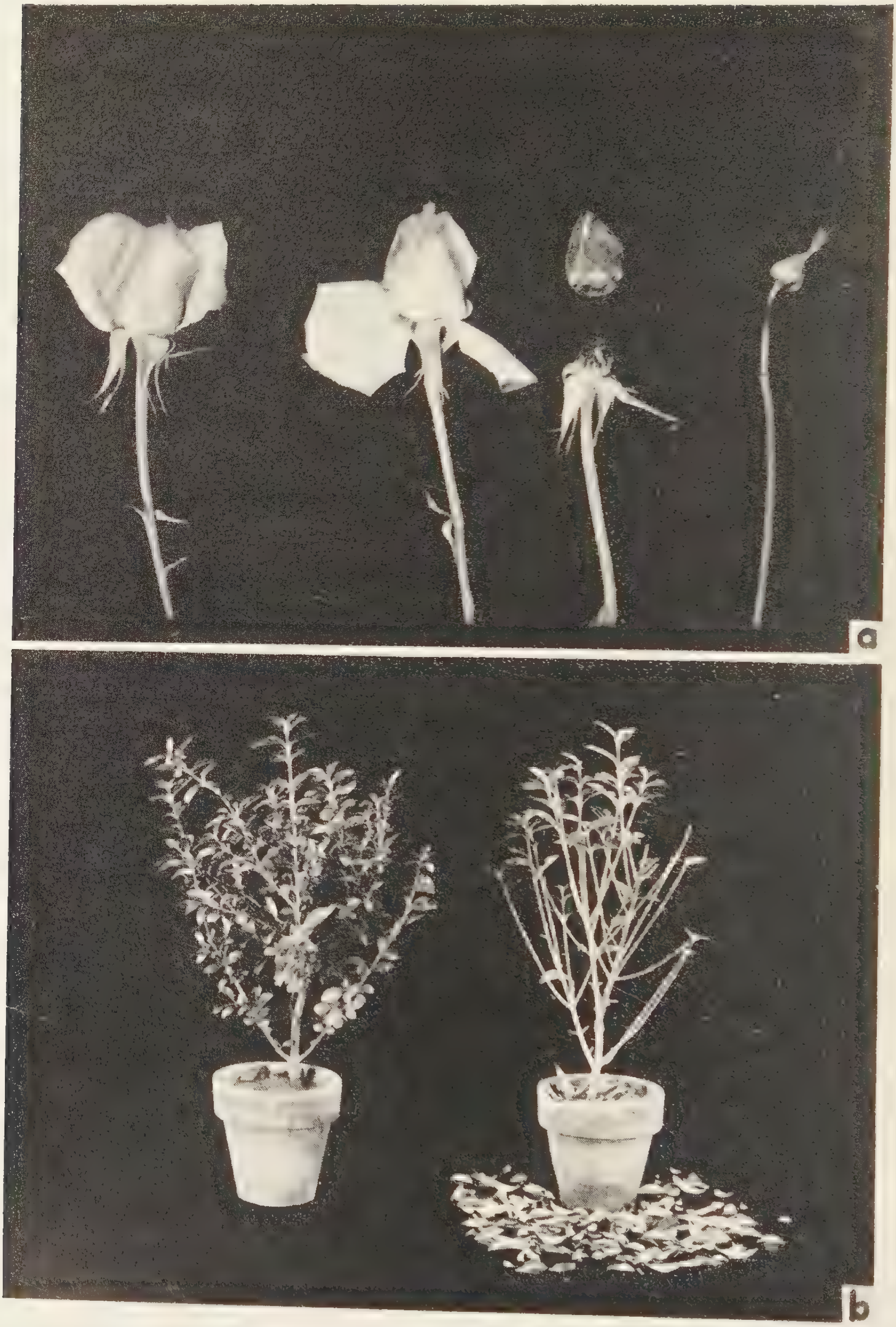


FIGURE 1. Injurious effects of mercury vapor on Briarcliff rose buds and on privet. FIGURE 1a shows the control rose bud at the left, and the different effects according to the stage of bud development when exposed to vapor. FIGURE 1b shows the privet plants, with the control on the left and the abscission of leaves from the plant at right after exposure to mercury vapor.

much injury on plants receiving $HgCl_2$ as on those receiving only water. At this time 14 treated and 14 control plants were enclosed in a muslin cage where only the previously treated plants received additional $HgCl_2$. An equal number of control plants were left in the open in the same house, which was well ventilated thereafter, and all injured buds were removed from these plants, which were previously injured by mercury vapor but had not received $HgCl_2$. All plants in the muslin cage continued to show the flower injury, but the plants in the open recovered and produced normal flowers after 21 days.

Similar tests were carried out with potted roses in glass cages (3 × 3 × 4 ft.). The results were the same; nontreated roses showed as much injury after 6 days as those receiving $HgCl_2$ via the soil. The roses in the control glass cage grew normally and produced pink flowers characteristic of the Briarcliff variety.

When potted Briarcliff roses were treated with $HgCl_2$ and placed immediately in a well-ventilated house, symptoms of mercury-vapor injury did not appear. Injury to roses occurred only on those plants exposed to a source of mercury in a confined atmosphere. Tankage and $HgCl_2$, used alone or when both were mixed with soil, resulted in greater injury than the same amount of $HgCl_2$ used alone. Tankage alone did not cause injury. Placing a small pan of metallic mercury in a cage with potted roses caused severe injury in 20 hours: all leaves were killed, and the flower buds showed patches of injured tissue. Under similar conditions a pan of $HgCl_2$ solution caused slight injury. Notwithstanding that slight injury occurred in this 1 test, it was concluded[2] that injury to roses resulting from the addition of $HgCl_2$ to the soil was caused mainly by metallic mercury in vapor form. Sufficient $HgCl_2$ was reduced to metallic mercury by the organic matter in the soil to furnish a toxic quantity of metallic mercury vapor. The results of later and more comprehensive tests supported this concept and constituted the subject of a second report,[6] to be discussed later.

In 1933 Ratsek[3] confirmed the results of Zimmerman and Crocker with respect to the injury of greenhouse roses by emanations from soil treated with $HgCl_2$. The salt was applied at the rate of 1 lb./400 $ft.^2$ of soil to some of the benches and then washed in with water. After 1 week, roses in all the benches showed symptoms similar to those described by Zimmerman and Crocker.[2] Ninety per cent of the flowers dried without opening, and the others exhibited a bleached pale-pink color. Symptoms not previously reported were as follows: the small flower buds yellowed and fell off; an excessive number of abnormally short axillary shoots with light green leaves developed later below the injured area and formed few or no flower buds; the leaves on many of the stems "drooped" and eventually became olive green in color and leathery in texture; 1 or more breaks in the petiole widened, lengthened, and corked over, resembling intumescences, and sometimes they extended into the midvein of leaflets; and the terminal leaflet of drooped leaves turned yellow, an effect followed by yellowing of the other leaflets and abscission of the leaf. The varieties Hollywood and Gloria Mundi showed these symptoms on the benches treated with $HgCl_2$, but only Briarcliff showed these symptoms on the 4 untreated benches. The Joanna Hill variety was not affected.

TABLE 2

MERCURY CONTENT OF LEAVES FROM ROSES EXPOSED IN A GLASS CASE TO METALLIC MERCURY OR TO MERCURIC CHLORIDE ($HgCl_2$) ALONE, ATOMIZED ON SOIL, AND IN THE PRESENCE AND ABSENCE OF LIGHT*

Treatment and conditions during treatment	Surface area of mercury (cm.^{2})	Mercury in dry leaves, p.p.m.	
		Joanna Hill	Briarcliff
Plants exposed 6 days to metallic mercury			
	0	0.0	0.0
Night temperature 68° F.	1	0.6	1.1
Day temperature 80° to 85° F.	4	3.6	6.9
	9	12.4	17.2
	16	39.1	116.9
Plants exposed 4 days to mercuric chloride			
Control			0.0
$HgCl_2$ atomized on glass plate, then dried**			291.5
Same, but case covered with black cloth			16.4
$HgCl_2$ atomized on soil, washed in with water**			177.0
Same, but case covered with black cloth			7.5

* Compiled from data in Ratsek's report.[3]

** Temperature in light at times 18° F. higher than in dark on 2 of 4 days.

In 1 test, Ratsek enclosed the tops of Briarcliff roses in cellophane bags with mercury, and with $HgCl_2$, alone or with soil, for 48 hours. The mercury caused the leaves to absciss in 24 to 48 hours. The $HgCl_2$ had only a slight effect and caused the least damage of the 3 treatments. Eventually, however, the leaflets thickened, and lesions appeared on the petioles of leaves exposed to $HgCl_2$.

Ratsek[2] was the first to show that abnormally high amounts of mercury could be recovered from rose leaves exposed to emanations from metallic mercury, from dry $HgCl_2$, and from soil moistened with $HgCl_2$. The mercury content of leaves increased with increasing surface area of mercury, and the Briarcliff variety accumulated more than did the Joanna Hill (TABLE 2). In 1867 Boussingault[7] showed that the amount of mercury vapor fixed by a suspended strip of gold increased with the increasing surface area of metallic mercury.

Mercury vapors induced the same symptoms on Briarcliff roses as those that appeared on the bench-plot roses treated with $HgCl_2$. Flower buds exposed to 4 cm.^{2} or more of mercury failed to open and turned black. An area of 9 cm.^{2} or more caused abscission of the leaves. The Joanna Hill variety showed no injury, and all flower buds opened and appeared normal. The greater resistance of Joanna Hill was attributed to the lesser accumulation of mercury. It was later shown by Zimmerman and Crocker[6] that the accumulation of mercury in leaves of 10 species of plants had no relation to their relative susceptibility to mercury vapor.

Ratsek's exposure of Briarcliff roses for 4 days in a glass case (16 × 16 × 24 in.) to mercuric chloride atomized and dried on a glass plate (33 mg. residue) resulted in a greater accumulation of mercury in the leaves than did a similar exposure to the same quantity of the compound atomized on an equal area of soil and washed in with water (TABLE 2). There was a much greater accumulation of mercury in the leaves exposed to light as compared with the leaves kept in darkness. These results were the principal basis for concluding that soil did not reduce mercuric chloride to the metallic state, as postulated by Zimmerman and Crocker[2]; consequently, Ratsek claimed that the injury to Briarcliff roses was caused by vaporized mercuric chloride. It should be noted that in one of Ratsek's previous tests the rose shoots enclosed with mercuric chloride in cellophane bags showed less injury then the shoots exposed to a mixture of soil and mercuric chloride.

In the preceding test the effect of light (TABLE 2) was more than 10 times as great as the effect of soil. Since the temperature at times was 18° F. higher in the glass cases exposed to light than in the cases kept in darkness, the much greater accumulation of mercury in rose leaves exposed to light was probably due primarily, if not entirely, to the higher temperature. Recognizing this possibility, Ratsek[3] stated that, if the difference were mainly due to temperature, "it is also possible that mercuric chloride, as such, may cause the injury." When the leaves were collected for analysis, however, no mention was made of injury to the leaves or to the flower buds in this particular test. Furthermore, an elevation of 18° F. in temperature would increase the vaporization of mercury, and to a greater extent than the vaporization of mercuric chloride.[6] Although the accumulation of mercury in the leaves of roses exposed to mercury and to mercuric chloride furnished evidence that the emanations in both cases contained mercury, there was no evidence to support the statement that mercuric chloride in soil was not reduced to the metallic state. A test for mercury in the air was not made by chemical or physical methods.

The work started by Zimmerman and Crocker in 1932[2] was continued, and a second report containing additional results appeared in 1934.[6] A description of the previous results is also given in the second report, together with much new information relating to the detection of mercury vapor emanating from mercury and from soil treated with organic and inorganic compounds of mercury, and to the recovery of mercury from leaves of different species of plants exposed to known sources of mercury.

In addition to the use of 398 rose plants in 14 different tests, species of plants representing 74 other genera were exposed to soil moistened with 1 per cent $HgCl_2$. The species most susceptible to mercury vapor were broad bean (*Vicia faba*), butterfly weed (*Asclepias tuberosa*), oxalis (*Oxalis corniculata*), sunflower (*Helianthus debilis*), and rose (Briarcliff, Columbia, Coolidge, Killarney, Madame Butterfly, Pernet, Premier Supreme, Talisman, and Templar varieties). Among the 10 relatively resistant species were aloe (*Aloe arborescens*), croton (*Codiaeum* sp.), English ivy (*Hedera helix*), oak (*Quercus* sp.), and pachysandra (*Pachysandra terminalis*). Some of the species of intermediate susceptibility were peach (*Prunus persica*), privet (*Ligustrum* sp.), tomato (*Lycopersicon esculentum*), geranium (*Pelargonium* sp.), and Boston fern (*Nephrolepis exalta*).

Detailed descriptions of symptoms are given by Zimmerman and Crocker only for the rose, the peach, and the privet, which were regarded as representative of susceptible species in general. Symptoms of mercury-vapor injury are illustrated in the work cited for flowers of the Briarcliff rose (in color), for leaves of 10 other species, and for peach seedlings held at different temperatures. In general the older leaves and the older tissue on a given leaf were injured first, and here the degree of injury was greatest. The youngest leaves and the growing tips of shoots were seldom injured unless the plant was killed.

Peach seedlings were used to determine the effect of temperature on the rate of injury from mercury vapor. In 1 series 5 ml. of mercury was placed with the plant under a bell jar. In the other series the plant was exposed under a bell jar to 400 ml. of tankage moistened with 200 ml. of 0.05 per cent $HgCl_2$. The peach seedlings held in darkness at 35° and 40° F. in rooms with controlled temperature were not injured, whereas those held at 75° F. were killed. Slight to moderate injury occurred at 50° to 60° F., including abscission of some lower leaves, but the plants in both series of tests recovered and appeared normal after 2 months. Apparently, toxic amounts of mercury were not translocated into the shoots that developed after treatment. These results showed that the degree of injury increased with increasing temperature, from no injury at 40° F. to death of the plant at 75° F. This important influence of temperature was presumably due to the effect of temperature on the vapor pressure of mercury, which likewise increases with increasing temperature and at a considerably faster rate than the vapor pressure of $HgCl_2$.[6]

Ratsek[3] reported 18 to 24 times as much mercury in rose leaves held in light as in those held in darkness (TABLE 2). The much higher temperature in light was no doubt responsible for this difference. With controlled temperatures Zimmerman and Crocker[6] found no effect of light on the accumulation of mercury in peach leaves exposed to soil moistened with $HgCl_2$ (p. 181). The amount of mercury in 8 gm. of dry leaves was determined by the precipitation method.[8] The amount of mercury fixed by gold was also shown by Boussingault to be a function of temperature (TABLE 1).

Ratsek suggested that the varietal differences in susceptibility to injury by mercury vapor (TABLE 2) were due to the relative amount of mercury accumulated in the leaves. Thus the Joanna Hill rose was relatively resistant because of the lesser amount of mercury accumulated as compared with the more susceptible Briarcliff variety. On the basis of the results obtained with 10 different species or varieties (including the rose), Zimmerman and Crocker[6] showed that the susceptibility of species or varieties, or of different tissues on the same plant, had no relation to the amount of mercury accumulated. For example, the mercury content of leaves (parts per million dry weight) was 317 for the Briarcliff rose, 808 for the Coolidge rose, and 2405 to 3747 for different-aged leaves of Turkish tobacco. Briarcliff is more susceptible than Coolidge, and both roses are more susceptible than tobacco. Similarly, the relative susceptibility of different species of plants to volatile fluorides, such as hydrogen fluoride or silicon tetrafluoride, has no close relation to the amount of fluorine accumulated in leaves,[9] although many of the more resistant varieties of gladiolus accumulate the most fluorine.

Zimmerman and Crocker[6] were the first to use a chemical method for detecting mercury vapor in the air surrounding plants. Air was drawn for 72 hours through a bell jar containing a 400-ml. beaker of soil moistened with $HgCl_2$, then over a peach seedling in a second bell jar, and finally passed over gold leaf at the exit. The gold was transferred to the bottom of a small test tube, the top of which was then drawn out to a fine capillary. Heat was applied to drive off the mercury which, if present, would vaporize and condense on the upper walls of the test tube. The upper part of the test tube was cut off and placed in a tube of slightly larger size over a crystal of iodine. When elemental mercury was present, it would react with iodine to form brilliant red mercuric iodide. Amounts of condensed mercury too small to be seen with the naked eye produced a conspicuous color. By this method it was demonstrated that the air that caused injury to peach leaves gave a positive test for mercury.

Similar results were obtained when $HgCl_2$, mercurous chloride, mercuric cyanide, and each of 3 organic mercury fungicides were added to tankage. The amount of injury to the plant and the amount of mercury fixed by gold were much greater with tankage than with soil. When $HgCl_2$ was atomized and dried on a glass plate, however, the plant was injured, and mercury was detected in the air passing over the plant; but when air was similarly drawn for 10 instead of 72 hours over the glass plate containing the deposit of $HgCl_2$, without a plant in the bell jar, a positive test for mercury was not obtained. Mercurous chloride on a glass plate neither injured the plant nor gave a positive test for mercury in the air, but it was highly effective when added to soil or to tankage, thus verifying the results obtained in 1797.[1] Soil or tankage alone gave negative results. It was previously mentioned that Ratsek obtained toxic emanations from a deposit of $HgCl_2$ on a glass plate, and mercury was recovered from the injured rose leaves (TABLE 2).

A modification of the procedure just described was used to detect elemental mercury in the emanations from soil moistened with any 1 of 6 organic and 7 inorganic compounds of mercury. Air was drawn for 10 hours through an absorption tower filled with the treated soil and then over gold leaf in an exit tube. All compounds gave a positive test, indicating that some of the mercury was reduced to the metallic state. Crystals of $HgCl_2$ gave a negative test, as in the case of $HgCl_2$ on a glass plate in a 10-hour test. It would appear, then, that within 10 hours the amount of mercury emanating from $HgCl_2$ is not sufficient to injure plants or to be detected by the gold-leaf test. This is in contrast to the injurious effects on plants and a positive test for elemental mercury obtained after 72 hours by the gold-leaf method. The results of Zimmerman and Crocker[2, 6] and Ratsek,[3] however, do not show to what extent, if any, the vapors of $HgCl_2$, as such, were involved in causing injury to roses in greenhouses where $HgCl_2$ was applied to the soil.

The results reported by Zimmerman and Crocker in 1934 are described briefly elsewhere.[9-11] A brief review of the reports on mercury-vapor injury to plants from 1797 to 1934 is given by Thomas.[9]

About 20 years later Butterfield (1954) reported injury to Better Times roses caused by emanations from greenhouse paint containing an organic mercury as a fungicide.[4] Two rose growers (Peirce Brothers, Inc., Waltham, Mass., and Arnold-Fisher Co., Woburn, Mass.) had used the mercury-containing paint only in certain houses. Symptoms of mercury-vapor injury similar to those described by Zimmerman and Crocker were seen on roses only in the houses where the mercury-containing paint was used. When the same paint was applied on August 30, 1954, to the interior surface of a rose house at the Waltham Field Station in Massachusetts, Peter's Briarcliff roses (a Columbia strain like Briarcliff and Better Times) showed some injury on September 19, and severe injury on September 25. The discolorations on flowers, peduncles, and on undeveloped buds that eventually turned brown without opening, resembled the injuries seen on roses in similarly painted houses at Peirce Brothers and at the Arnold-Fisher Co. Butterfield made no mention of injury to rose leaves.

A General Electric Company mercury-vapor detector showed a slight reading when it was held over a surface painted 24 hours previously and a high reading when held over a newly opened pail of paint. Butterfield also reviewed the toxic effects of mercury vapor on humans and described recommended protective and precautionary measures to be taken.

In 1955 Dimond and Stoddard[5] described symptoms of mercury-vapor injury on roses observed in commercial rose houses in Connecticut that were painted on the interior with a mercury-containing paint. These authors state that the symptoms were like those described by Zimmerman and Crocker.[6] In houses painted with a mercury-containing paint the petals of flowers contained 1.3 parts per million (p.p.m. fresh weight); the leaves 3.3 p.p.m. The concentration of mercury in the petals of normal flowers (not exposed to mercury-containing paint) was 0.2 p.p.m.; in leaves of normal plants, 0.07 p.p.m.

The presence of mercury in normal rose plants is of interest, since human tissue also contains mercury. Mercury is present in our food, the normal daily diet containing about 20 μg. The average content of mercury in human tissue, determined spectrographically, is given as 2.05 mg. 100 gm. of dry tissue, and as high as 12.7 mg. 100 gm. in kidney tissue.[12] In view of these findings it is probable that many plants, possibly all, contain mercury, and that different parts of the plant would contain different amounts of mercury. Ratsek reported no mercury in control rose leaves. Neither Ratsek nor Dimond and Stoddard mention the method of analyzing for mercury in plant tissues. Zimmerman and Crocker[6] used the standard precipitation method, which is not suitable for determining small amounts of mercury of the order of 1 p.p.m. or less on a dry-weight basis.

It was stated that the fungicide used in the paint was di-(phenylmercuric) dodecenyl succinate (DPMDS), and that such paints contained as much as 0.84 per cent by weight of the fungicide (active ingredient 21 per cent) that contains 10 per cent metallic mercury. The manufacturers of this fungicide,* known as Super Ad-It, state that 1 fluid ounce (U. S.) will protect up to 1 gallon of paint, and that if mildew conditions are severe, a double quantity should be used. No mention of possible phytotoxicity is made on the label.

Under experimental conditions, Dimond and Stoddard detected mercury vapor by physical, chemical, and biological methods. A vapor detector manufactured by General Electric Company was used for detecting, quantitatively, concentrations of mercury vapor in the range of 0.01 to 2.4 mg. of mercury per cubic meter of air. This instrument depends upon the absorption by mercury vapor of ultraviolet radiation of wave length 2537 A. Since the instrument failed to give a reading in the air around the injured roses in the house painted with mercury paint, the concentration of mercury vapor was less than 0.01 mg. per cubic meter of air. When various materials were applied to filter paper and sealed for 19 hours in screw-top tubes, however, the following results were obtained, involving the measurement of concentrations of mercury vapor greater than 0.01 mg. per cubic meter of air. The amount of mercury released from a mercury-paint coating increased with the area of the coating, as demonstrated by other investigators.[3, 6, 7] Enamel grinding oil and 6 other components in a greenhouse white paint increased the release of mercury from DPMDS. Likewise, several formulants of aluminum paints, including metal naphthenates, increased the release of mercury from DPMDS. Other workers[2, 6] showed that tankage was more effective than soil in releasing metallic mercury from compounds of mercury. Only Ratsek[3] was opposed to this concept. It is known also that many kinds of organic materials, such as sugars, turpentine, creosote, gelatin, and many vegetable and animal substances reduce compounds of mercury to the metallic state.[13]

---

* Nuodex Products Co., Inc., Elizabeth, N. J.

Lime sulfur was the only coating of several tested that greatly reduced or prevented the release of mercury vapor from paint containing DPMDS, and the effectiveness of 1 application in a commercial rose house lasted at least 5 months. The counteracting effect of sulfur on mercury vapor, as previously mentioned, was demonstrated in 1797[1] in tests involving the placement of sulfur separately from metallic mercury on the wall of a bell jar or by dusting sulfur on leaves of the mint test plant. Later (1867) Boussingault[7] showed that sulfur vapor reacted with mercury vapor to form mercuric sulfide, and that no free mercury vapor could be detected in the confined air.

Dimond and Stoddard used the mercuric-iodide method in 1 test and the vapor detector in most tests for detecting mercury vapor emanating from deposits on filter paper placed in the bottom of screw-cap tubes. The results showed that mercury vapor increased with increasing surface area and increasing amounts of mercury-containing substances, and that certain components of paint, such as enamel grinding oil and metal naphthenates, increased the release of mercury from DPMDS. On the other hand, lime-sulfur paste was the only overcoating of several tried that greatly reduced or prevented the release of mercury vapor from a film of standard white mercury paint prepared in their laboratory (0.525 per cent DPMDS by weight). It was concluded that DPMDS in paints decomposes to mercury, which is then released from the paint film as mercury vapor. This would account for the injury observed in the commercial rose houses.

The results just described indicate that mercury vapor is given off from paint containing the mercury fungicide (DPMDS) much the same as from soil to which a compound of mercury has been added. There is 1 important difference between the results obtained by Zimmerman and Crocker[6] and Dimond and Stoddard,[5] however, namely, that the latter workers did not detect injurious concentrations of mercury vapor in the air surrounding the test plants. The vapor detector was not sufficiently sensitive to give a positive reading in the air surrounding the roses in the commercial houses in Connecticut, where mercury paint had caused severe injury to Better Times roses. Both Dimond and Stoddard[5] and Butterfield[4] reported that the vapor detector gave a slight reading only when held close to a 24-hour-old mercury paint film. Boussingault demonstrated a marked decrease in the amount of mercury vapor in the air with increasing distance from the surface of metallic mercury (TABLE 1).

Tests[5] in which cut flowers of Better Times roses were confined in plastic containers with dried paint films gave variable results and proved unsatisfactory for demonstrating mercury injury on the basis of premature petal drop. The use of petal drop alone as a characteristic symptom of mercury-vapor injury was not mentioned by previous investigators. Abscission tests with the pinto bean and the broad bean were not satisfactory for determining the relative effectiveness of various coatings as mercury-vapor barriers when applied over DPMDS paint. Also, the concentrations of mercury vapor measured by the vapor detector were not correlated with those that injured roses or other species of plants, as was demonstrated by Zimmerman and Crocker[6] by means of the mercuric iodide test.

Dimond and Stoddard[5] suggested that mercury, after removal of the plant to an atmosphere free of mercury, is translocated from the vegetative parts or from the leaves of injured roses to the developing buds. This conclusion was based on the results obtained from the transfer of 1 Better Times rose plant free of soil from a commercial rose house painted with mercury paint to the Connecticut Agricultural Experiment Station, where it was planted in sand. After 3 months the new flowers showed discolorations typical of mercury-vapor injury. The petals of these flowers contained 0.4 p.p.m. more mercury than normal flowers.

On page 5 of the cited work, the same workers also suggested that mercury is taken by the plant from the soil, but they incorrectly referred to the results of Zimmerman and Crocker[6] as demonstrating such an uptake. The reports thus far cited[1-7] do not refer to the determination of mercury in soil. Thus it is not known whether the exposure of plants to a source of mercury in the soil and in the air results in a greater accumulation of mercury in the leaves as compared with the exposure of similar plants only to mercury in the air. It has already been mentioned that the visible injury on arterial parts of the plants was the same for the 2 sets of plants.[3, 6] Ratsek,[3] however, stated that the injury was the same for Briarcliff roses throughout the house, but not for the Gloria Mundi and Hollywood varieties, which exhibited injury only on the plants in the soil to which $HgCl_2$ had been added. This could be interpreted as an indication that vapors of the compound ($HgCl_2$) were contributory, that mercury in some form was taken up by the plant from the soil, or that both were involved. Unfortunately, an analysis of the leaves was not made, so that the question of mercury uptake by the plant from soil remains unsettled.

As additional evidence of mercury uptake by the plant from soil, various combinations of transplanting new and old roses in new and old soil in a commercial rose house painted with mercury paint are cited.[5] The authors concluded that "New plants in old soil apparently absorbed some mercury from the soil, as indicated by the lower rate of growth and reduced flower production." A similar exchange of plants and soil was not made in a house not painted with mercury paint. Presumably, any adverse effects on the new plants and delayed growth on the old plants could be accounted for by emanations from the mercury paint. Zimmerman and Crocker[6] stated that the different species of plants injured by mercury vapor recovered after removal to a normal atmosphere and produced new growth that appeared normal and, in the case of the rose, produced flowers of normal color. The rate and degree of recovery depended upon the extent of injury and the species. The recovery of the injured plants is not described in sufficient detail in any published report to give a comprehensive picture of what is meant by normal recovery or, in the case of rose, the production of normal flowers. Quantitative data are entirely lacking.

Effects of Mercury in Paint

The roses in the greenhouses of Peirce Brothers and of the Arnold-Fisher Co. that Butterfield[4] described as exhibiting symptoms of mercury-vapor injury were also observed by the senior author of this paper in late 1954. Symptoms on Better Times roses were similar to those described by Zimmerman and Crocker[2, 6] and Ratsek[7] for Briarcliff roses injured by mercury vapor. The conclusion that mercury vapor was the probable cause of the injury seen on Better Times roses was in agreement with the view held by Butterfield. The rose houses referred to in this case were painted on the interior with a mildew-retarding white paint. The active fungicidal ingredient was claimed to be di-(phenylmercuric) dodecenyl succinate, sold under the name of Super Ad-It. Some of this paint was brought to Yonkers, N. Y., to be tested for the presence of mercury and for the effect of mercury emanations, especially on Better Times roses.

The presence of mercury in the test paint (referred to hereafter as mercury paint) and its absence in the control paint were established by the precipitation method of analysis.[5] An outside white paint manufactured by the Pittsburgh Plate Glass Company, Pittsburgh, Pa., was used as the control paint. A similar analysis of Super Ad-It showed 9.7 per cent mercury as the metal.

Flexible pieces of veneer wood 7 to 12 in. wide and 8 to 12 in. long were painted on both sides with 1 coat of paint, dried for 2 days or longer, and then shaped into half cylinders and secured by circular metal bands (7 to 8 in. in diameter) at the top and bottom. When placed in a pliofilm bag, each painted section of wood was secured, together with a thermometer, by a cord to the top of the bag, so that the entire unit could be moved upward if an unusually rapid elongation of the flower shoot occurred during the period of exposure.

Newly-grafted Better Times roses planted in October 1954 in 4-gal. buckets were used in a series of 17 tests, starting the following December and using the same paint films until November 1955. The entire plants were enclosed, but not sealed, with the test material in 22-l. bell jars; alternatively, the tops of one or more shoots were enclosed with the test material in Vinylite or polyethylene bags. A location was selected in a greenhouse where large light reflectors furnished intermittent shade from 9:00 A.M. to 2:00 P.M. Under these conditions the maximum temperatures inside the enclosures generally were 95° to 115° F. between 10:00 A.M. and 2:00 P.M. on sunny days and 70° to 85° F. on days when the sun failed to shine. Plants or parts of plants were generally exposed to mercury paint or to the mercury fungicide (Super Ad-It) for a period of 1 week.

Better Times roses and tomato plants (*Lycopersicon esculentum*) were exposed to metallic mercury as well as to mercury paint. Mint (*Menthá piperita*) was exposed to metallic mercury alone and to mercury distributed in moist soil contained in a Petri dish. Plants and parts of plants were exposed to metallic mercury for periods of 1 to 3 days.

The symptoms of injury and the order in which they appeared on Better Times rose shoots exposed to mercury paint for a period of 1 week were as follows:

After 1 week. The abnormal color of the flower buds varied considerably in different tests, but was generally faded or off-color, such as pink, bluish, lavender, or cream, on the distal part of the petals, and was most pronounced at the margins. The bases of the outer petals were generally whitish or greenish white at this time. Mature or nearly mature flower buds frequently opened and resembled the control flowers in color, but sometimes they had shorter petals. Young flower buds not showing the color of petals and less than one-fourth in. in diameter exhibited little or no development (7 to 14 days) and were sometimes a yellowish green (7 to 19 days). Immature leaves were retarded in development; the youngest were the most affected (5 to 13 days). A slight declination of one or more leaves, including a downward curvature of the terminal leaflet, sometimes occurred (7 to 19 days).

After 2 weeks. An abnormal discoloration of the flower buds or flowers either appeared or, if present at the end of 1 week, became more pronounced and included browning (14 to 27 days). Retarded development of the flower buds and young leaves was more noticeable. Some buds had not opened, whereas comparable buds on the control plants were fully open. A slight yellowing of the peduncle of unopened, discolored flower buds sometimes occurred (14 to 18 days). Declination of the leaves was more noticeable, and more leaves showed this response. The downward curvature of the terminal leaflets was also more pronounced, and some side leaflets showed a slight downward curvature and were more rigid when touched than normal leaflets, giving the appearance that Ratsek referred to as a "droop."

After 3 weeks. Discolorations were more pronounced on the flower buds, and they resembled those shown in FIGURE 1. Buds that showed browning during the second week were now entirely brown or purplish brown. Very small flower buds that showed little or no development after 1 week were either dark brown and brittle or had abscissed. Peduncles were yellow (15 to 18 days) or nearly black below flower buds that had not opened or had abscissed (19 to 30 days), resembling the symptoms shown at right in FIGURE 1. The midveins and petiolets of some leaflets and the petioles and midribs of some leaves had turned light green, especially on the declined leaves with downward-curved leaflets. Declined leaves with down-curved leaflets showed no recovery up to this time (or later).

After 4 weeks. Relatively little change was observed in the responses previously described, except that the blackening of peduncles was more pronounced. Sometimes an axillary bud started to grow (27 to 50 days or longer).

After 5 weeks. The growth of a few axillary buds started, but the 2 upper buds on the flower shoot did not always grow. Proliferation of the petioles and midribs started as small longitudinal breaks in the tissue. Similar lesions on the lower side of the midveins of leaflets generally followed in time, but did not always occur. Browning of these lesions usually occurred in a few days. Axillary bud growth on noticeably injured flower shoots was abnormal with respect to the excessive number of buds starting to grow, the short length of the shoot, and the small number and small size of leaves eventually produced (a normal flower shoot was not produced from buds in the axil of declined leaves that exhibited marked downward curvature of the leaflets, as indicated on the symptomology after 6 to 7 weeks).

After 6 to 7 weeks. Proliferation and browning of lesions on petioles, midribs, and midveins were more pronounced. The midveins and secondary veins of some leaflets became light green, yellow, or brown and progressed in the order named (FIGURE 2). Discoloration was most pronounced in the lower

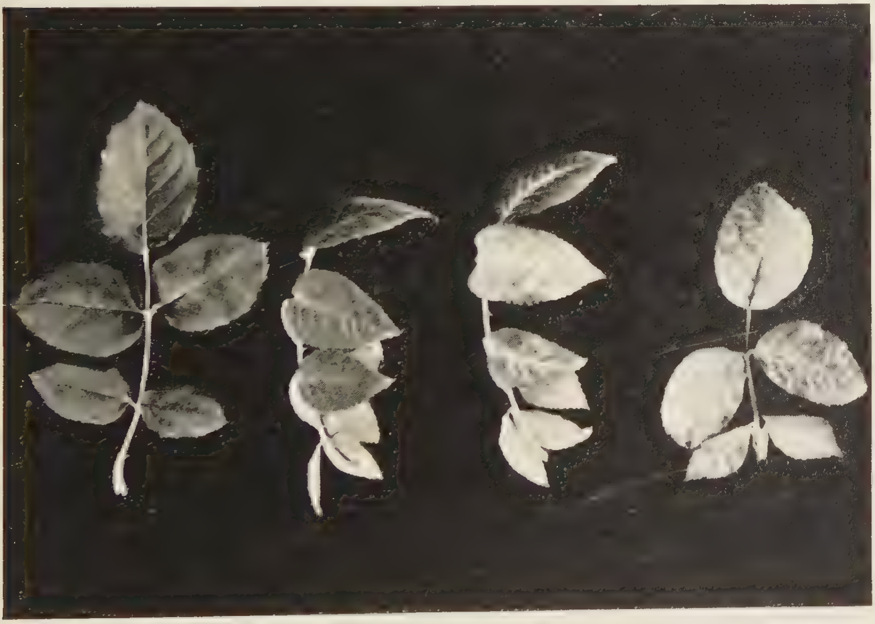


FIGURE 2. Characteristic symptoms of mercury-vapor injury on leaves of the Better Times rose, showing the curvature and stiffness of the leaflets and the premature yellowing and browning of the veins. The control leaf is at the left. The 3 leaves on the right were removed from the shoot exposed to mercury-containing paint on the plant shown in FIGURE 3.

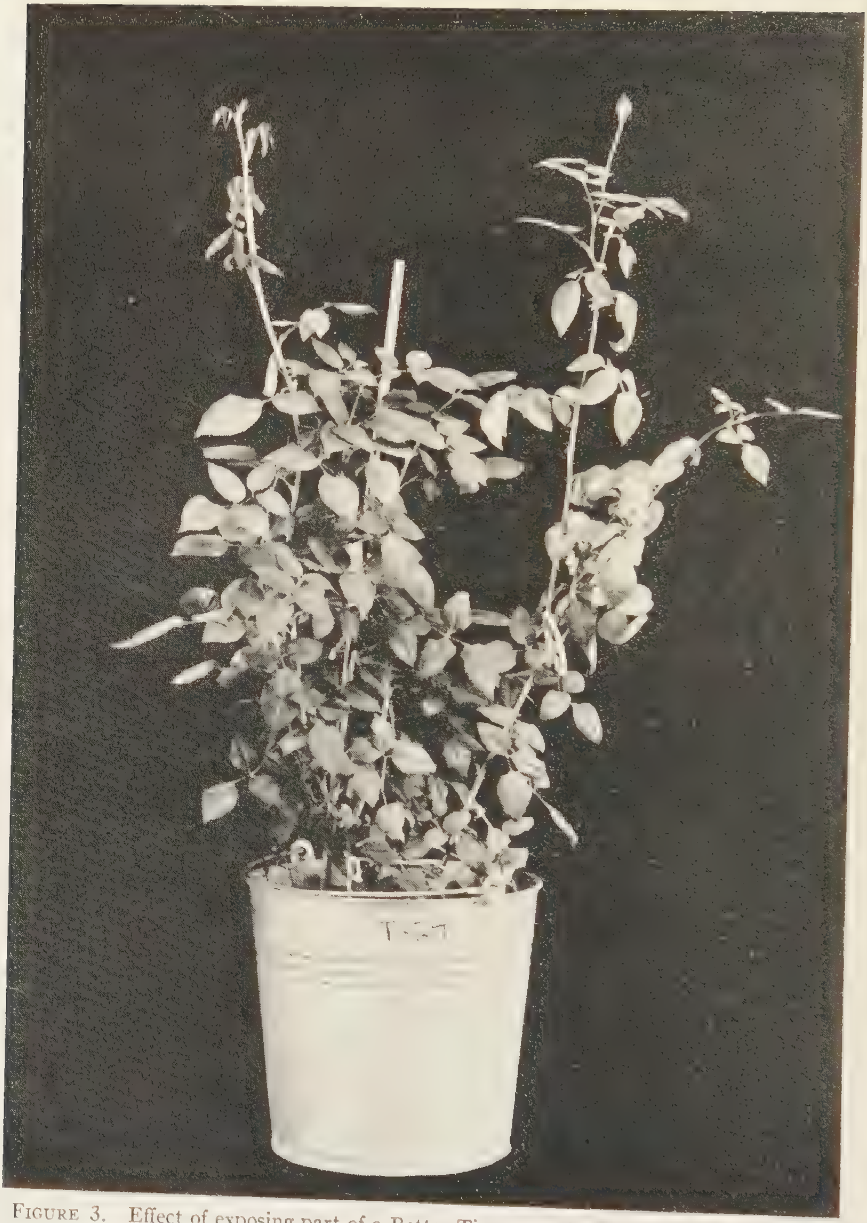


Figure 3. Effect of exposing part of a Better Times rose for 7 days to vapors from mercury-containing paint. The upper part of 1 shoot from the center of the plant was enclosed January 28, 1955, in a pliofilm bag with a piece of wood painted with control paint, and the upper part of the 2 shoots at the right were similarly exposed to mercury containing paint. The 2 shoots at the left were not enclosed. Symptoms of mercury vapor injury appeared only on the leaves and the young flower buds of the shoots at the right, which were exposed to the mercury containing paint. There was no visible evidence of translocation of mercury when the plant was photographed on March 17, 1955, or subsequently.

part of the midveins and secondary veins. Yellowing of some leaflets started, and a few leaflets had turned light yellow or nearly white. A few leaves or leaflets had abscissed prematurely. With the premature abscission of leaves it became apparent that the declination of leaves and the curvature of leaflets was a permanent response. Examples of leaf curvature are shown on the treated shoot in FIGURE 3 and, when removed for photographing, in FIGURE 2. Parts of the plant exposed to mercury paint had not produced normal flowering shoots at this time. Blind shoots 8 in. or less in length or small flowering shoots similar to that shown in FIGURE 3 were sometimes produced.

Exposure of the entire plant to mercury paint eventually resulted in severe injury, especially to the upper part of shoots. In this case new flower shoots usually grew from the lower part of the plant (FIGURES 4 and 5). All shoots were not equally affected, but there was no consistent relation to the distance from the painted wood.

The symptoms just described were not observed on Better Times roses exposed under similar conditions to the control paint. Flowers that opened during the period of exposure varied from light to dark red, and they did not remain in good condition as long as flowers that were not held in the confined atmosphere of bell jars and pliofilm bags. The fading of flower color was presumably due to the relatively high temperatures reached during midday in the bell jars and pliofilm bags. In contrast, the flower buds that were not mature enough to open during treatment did not fade in color when exposed to the control paint. After removal of the bell jars and pliofilm bags there was no noticeable difference in the rate of petal drop from noninjured flowers that opened during the period of exposure to control paint and to mercury paint.

In the present tests the symptoms on Better Times rose buds exposed to mercury paint agree with those described by Zimmerman and Crocker[2, 6] and by Ratsek[3] for Briarcliff flower buds. The symptoms on the leaves were much the same as those described by Ratsek. Zimmerman and Crocker did not describe the characteristic curvatures and the various discolorations on the rose leaves that were induced by mercury paint in all of the present tests, regardless of whether the symptoms on the flower buds were well defined. Under the conditions used in the present tests, however, insufficient mercury vapor emanated from mercury paint to kill or cause the abscission of leaves during or shortly after treatment. Furthermore, the premature abscission of young or middle-aged leaves after several weeks did not occur until after the leaves had exhibited noticeable curvatures, a lighter green color, and a stiff, leathery texture. Yellowing and abscission of individual leaflets varied considerably and did not always follow the order first of the terminal and progressively to the basal leaflets, as described by Ratsek.

The minimum effects of mercury vapor on flower buds were a delay in the development of the very young buds and, at most, a slight discoloration or fading of such petal color as eventually developed. Symptoms on the leaves were generally better defined, and consequently served as a more reliable criterion of mercury-vapor injury than the symptoms on flower buds. In the absence of flower buds the leaves of Better Times roses could therefore serve as detectors of threshold concentrations of mercury vapor.

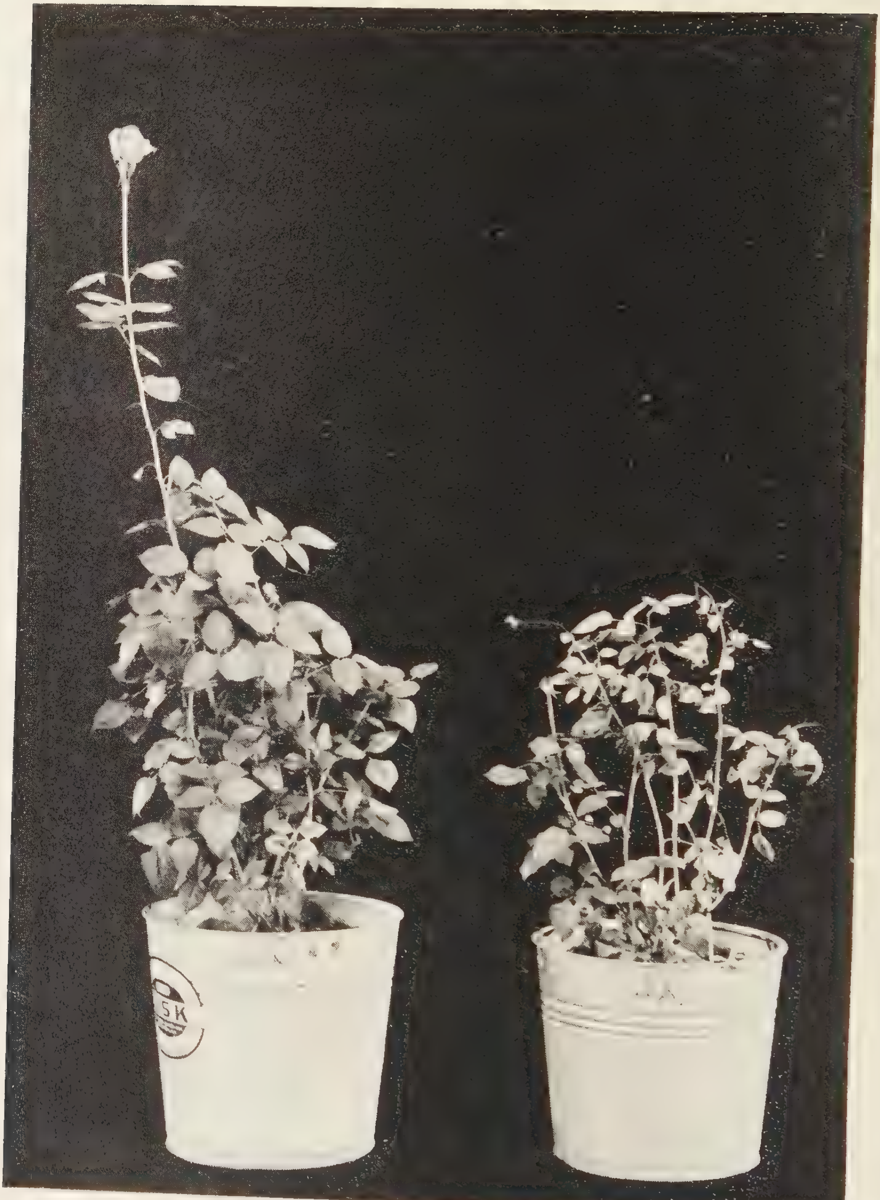


FIGURE 4. Better Times roses 45 days after a 7-day exposure to vapors from the control paint (left) and the mercury containing paint (right). The treatment was the same as that described in the case of the plants in FIGURE 5, starting December 31, 1954. The entire plant at the right was retarded in growth and development.

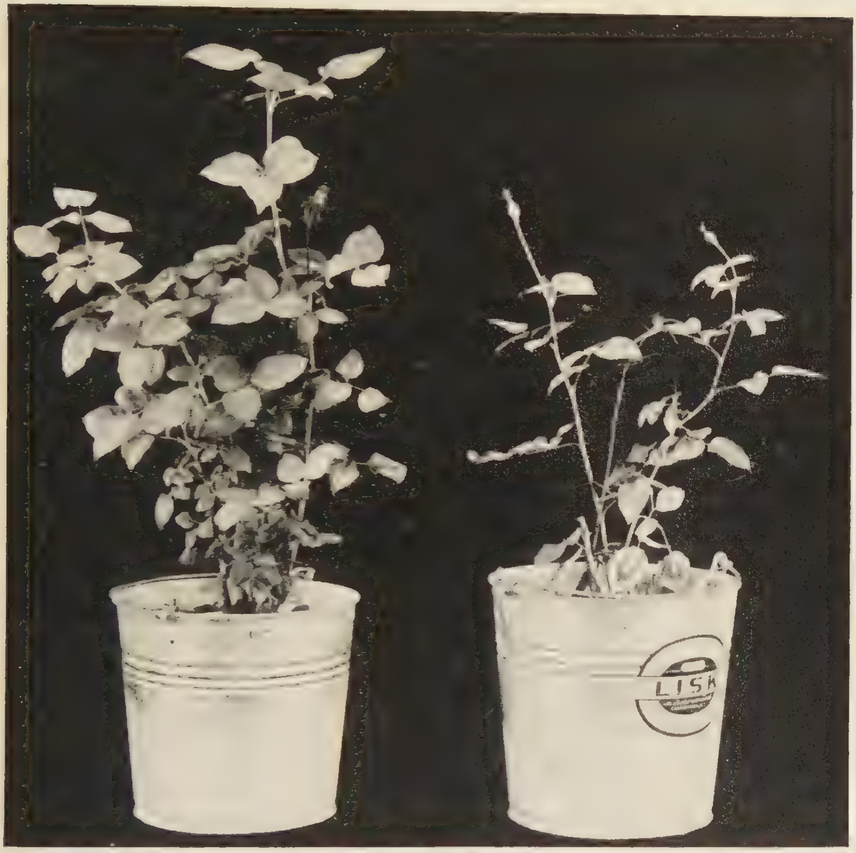


FIGURE 5. Better Times roses 3½ months after a 7-day exposure to vapors from control white paint (left) and vapors of a mercury containing paint (right). Each plant was enclosed with a piece of painted wood under a bell jar on December 1, 1954, when the shoots from the newly grafted plants were 5 to 8 in. long. Most of the original shoots were badly injured or killed, so that subsequent shoot growth was from the lower part of the plant. The temperatures reached 95° to 115° F. at midday on sunny days.

One test involved a 3-day exposure of young shoots of Better Times roses enclosed in pliofilm bags to mercury paint. One plant was placed in a partially shaded area where the maximum temperature inside the bag (left open at the bottom) was 75°, 88°, and 103° F. on 3 successive days. Five leaves on this shoot developed a moderate downward curvature of leaflets slowly over a period of several weeks. At the end of 2 months, lesions appeared on the petiole and midrib of 2 leaves. The only flower bud that opened was normal in size and color. Two young shoots on the other plant were similarly exposed to mercury paint where the maximum temperatures on successive days reached 86°, 112°, and 120° F. Marked symptoms of mercury-vapor injury developed on these shoots, including killing of the flower buds, retarded elongation of shoots (much shorter internodes), corking over of the middle part of the stunted stem, retarded expansion of immature leaves, declination of leaves, extreme downward curvature of leaflets, lesions on the petiole and midribs of leaves, premature yellowing of leaflets, and a lack of normal bud development from the treated part of the shoots.

Tests with metallic mercury induced in Better Times roses all of the symptoms caused by emanations from the mercury paint and, in addition, caused the abscission of leaves and leaflets during or shortly after an exposure period of 1 to 3 days, as illustrated in the case of privet (FIGURE 1). The longer periods of exposure to a mercury surface area of one-half-in. diameter caused a killing of parts of leaves, including spotting and speckling. The older leaves and leaflets of the tomato plant were also speckled much as were the rose leaves and, in addition, small spots occurred in the angle where side veins joined the midvein of the leaflets. The tomato plant, however, was less sensitive to mercury paint than was the rose. When potted plants of these 2 species were enclosed with mercury paint under a bell jar, the rose developed typical discoloration on its flower buds and exhibited curvature of leaves at the end of 2 weeks, whereas the tomato was neither marked nor retarded in growth. The tomato did not tolerate high temperatures as well as did the rose.

When Better Times rose shoots were exposed to emanations from the fungicide, Super Ad-It, the symptoms on the flower buds and leaves that developed afterward were the same as those caused by mercury paint. In this case 0.5 ml. of the undiluted Super Ad-It was deposited and dried on filter paper (14.2 in.^{2}) or in a porcelain dish (3.75 in.^{2}). No part of the plant touched the fungicide residue. After 2 months all leaves on the treated portion of the stem had abscissed, and only small leaves grew from the axillary buds, but the rest of the plant continued to grow normally and to produce normal flowers, indicating little or no translocation of mercury to the noncovered part of the plant.

Since there are no reports later than 1797 relating to the addition of metallic mercury to soil, a few tests were undertaken to determine whether mercury distributed in moist soil was toxic to peppermint plants. The mercury was scattered in the soil by thumb pressure after each of several thin layers of soil was added successively, but the top layer was only lightly firmed. The layer of soil in the Petri dish was 4 in. in diameter and 0.5 in. deep. Soil containing the mercury was enclosed for 24 hours with the mint plant (*Mentha piperita*) under a 10-l. bell jar at temperatures of 70° to 75° F.

In the first test, 1 ml. of mercury in the soil caused severe injury, killing all leaves but not the growing tips of the main shoots or the axillary shoots. Mercury (1 ml.) alone killed most of the leaves. When the test was repeated with 0.05 ml. of mercury, only a few leaves exhibited purplish-brown spots, but 2 to 3 pairs of leaves near the tips of the shoots showed a downward-arched curvature and were abnormally stiff, as described in the case of the rose. One pair of leaves on most of the axillary shoots also exhibited a similar curvature. Only partial recovery of the leaves to their normal position occurred after removal of the bell jar. As before, there was a slightly greater response from mercury in the soil, presumably due to the greater surface area of mercury consequent on breaking the mass into many small globules. The toxic effects obtained in these tests were to be expected on the basis of the previously mentioned concept that the reduction of mercury compounds in soil to the metallic state furnishes the source of the phytotoxic mercury vapor. The results just mentioned lend added support to this concept, but they are in disagreement with the conclusions of the Dutch chemists,[1] who observed no injury when metallic mercury was added to the soil of potted mint plants. The most likely explanation is that these particular plants were not placed under a bell jar, for all other results of the Dutch chemists and also of Boussingault[1] have been confirmed.

Although this report is concerned with the toxicity of mercury vapor to higher plants, the use of mercury fungicides deserves mention, as some of these have been used also as herbicides. A number of years ago it was observed that lawns treated with phenylmercury fungicides to control brown patch and several "fading out" diseases supported relatively little crabgrass. Eventually these same fungicides were used specifically as selective herbicides to control crabgrass without permanent damage to the desirable species of lawn grasses. The effectiveness of the phenylmercury compounds in killing crabgrass is assumed to depend upon thorough contact of the herbicide with the leaves of crabgrass plants.[14] No claim is made, in this instance or in connection with the use of phenylmercury compounds as fungicides, that mercury vapor is a contributory agent in the toxic action.

Summary and Conclusions

There is ample evidence to indicate that roses and other species of plants are injured by vapors from metallic mercury and from compounds of mercury, especially when the latter are mixed with organic matter such as that occurring in soil and in paint. Injury occurs when the plants are held in a confined atmosphere with the source of mercury. The extent of injury varies with temperature and other factors that influence the vaporization of mercury. Different species and varieties exhibit a great range of susceptibility. Certain symptoms of mercury-vapor injury differ from those known to be induced by other toxicants. Injuries caused by mercury vapor are indistinguishable from those caused by mercury compounds. The minimum effects of mercury vapor on Briarcliff and Better Times flower buds are associated with the characteristic curvatures of leaves. Recent results indicate that the leaves may be more sensitive than the flower buds of the Better Times rose.

The view generally accepted at present is that the phytotoxicity of mercury compounds is primarily due to the mercury vapor arising from mercury reduced to the metallic state, rather than to the vapor of the compound itself. Some organic substances are much more effective than others in releasing metallic mercury from mercury compounds in soil or in paint. Phytotoxic amounts of mercury vapor in the air surrounding plants have been detected by chemical methods, and abnormally large amounts of mercury have been recovered from the leaves of plants exposed to mercury and mercury compounds. There is no relation between the susceptibility of species or varieties to injury from mercury vapor and the mercury accumulated in leaves. Under certain conditions, however, the accumulation of amounts of mercury in leaves in excess of 3000 p.p.m. should, even in the absence of visible symptoms of mercury-vapor injury, be a warning to growers of edible greenhouse crops.

Mercury vapor has been detected by a spectrographic vapor detector in emanations close to paint films containing a mercury fungicide, but not in the air surrounding the injured plants. Paint films containing a mercury fungicide continue to release mercury vapor for at least a year. A brush coating of lime-sulfur paste over the mercury paint on the interior of greenhouses prevents the release of phytotoxic amounts of mercury vapor for periods of up to at least 5 months.

The speed of recovery of injured plants depends upon the extent of injury and the species. Badly injured roses may not produce normal growth or flowering for several months, and then only from the lower part of the plant. Slightly injured roses generally produce normal flower shoots from various parts of the plant within 6 weeks or less.

There are no conclusive data showing to what extent mercury in injured roses is translocated into shoots developing after the removal of the plant to a normal atmosphere. When part of a plant is exposed to phytotoxic amounts of mercury vapor, toxic effects are not seen on the rest of the plant. Likewise, there are no conclusive data to show that mercury is taken up by the plant from soil containing a source of mercury. Thus it is not known whether the addition of mercury compounds to soil results in a greater accumulation of mercury in the leaves, as compared with exposure of the plant only to mercury in the air. Quantitative data are lacking with respect to the possibility that soil exposed to mercury vapor absorbs mercury that is then taken up by the plant through the root system.

References

1. Boussingault, J.B.J.D. 1867. Sur l'action délétère que la vapeur émanant du mercure exerce sur les plantes. (Première partie.) Compt. rend. **64:** 924–929.
2. Zimmerman, P. W. & W. Crocker. 1933. The injurious effect of mercury vapor from bichloride of mercury in soil of rose houses. Florists Exchange Hort. Trade World. **81**(21): 13. *Also in* Boyce Thompson Inst. Prof. Pap. 1933. **1**(23): 222–225.
3. Ratsek, J. C. 1933. Injury to roses from mercuric chloride used in soil for pests. Florists Rev. **72**(1858): 11–12.
4. Butterfield, N. W. 1954. Roses affected by mercury compounds in greenhouse paint. Florists Exchange Hort. Trade World. **123**(18): 14.
5. Dimond, A. E. & E. M. Stoddard. 1955. Toxicity to greenhouse roses from paints containing mercury fungicides. Connecticut Agric. Exp. Sta. Bull. **595:** 19.
6. Zimmerman, P. W. & W. Crocker. 1934. Plant injury caused by vapors of mercury and compounds of mercury. Contribs. Boyce Thompson Inst. **6:** 167–187.
7. Boussingault, J. B. J. D. 1867. Sur l'action délétère que la vapeur émanant du mercure exerce sur les plantes. (Deuxième partie.) Compt. rend. **64:** 983–989.
8. Association of Official Agricultural Chemists. Committee on Editing Methods of Analysis. 1930. Official and tentative methods of analysis. 3rd ed. : 593. Washington, D. C.
9. Thomas, M. D. 1951. Gas damage to plants. Ann. Rev. Plant Physiol. **2:** 293–322.
10. Zimmerman, P. W. 1950. Impurities in the air and their influence on plant life. Proc. First National Air Pollution Symposium. : 135–141. Pasadena, Calif.

11. Zimmerman, P. W. 1955. Chemicals involved in air pollution and their effects upon vegetation. Proc. Governor's Conf. & Exhibit on Atmospheric Pollution. : 23–31. New Jersey State Dept. Health. Trenton, N. J. *Also in* Boyce Thompson Inst. Prof. Pap. 1955. **2**(14): 124–145.
12. Brown, E. A. 1955. The question of reactions to mercurial diuretics. Ann. Allergy. **13:** 131–159.
13. Mellor, J. W. 1923. A Comprehensive Treatise on Inorganic and Theoretical Chemistry. **4:** 1074. Longmans, Green. London, England.
14. Pirone, P. P. 1956. What's New in Gardening. : 254. Hanover House. Garden City, N. Y.

THE TOXICOLOGY OF INORGANIC MERCURY

By Leonard J. Goldwater
School of Public Health and Administrative Medicine, Columbia University, New York, N. Y.

In this paper an attempt will be made to cover briefly the more important effects of metallic mercury and of some of its inorganic compounds on the human organism. The pharmacology of inorganic mercury and its medicinal uses are covered by other contributions to this monograph. Even though compounds of organic mercury are of increasing importance as occupational health hazards, they do not fall within the scope of the present paper and, in any case, they are dealt with elsewhere in these pages.

Today human poisoning due to inorganic mercury is almost entirely accidental; rarely is it intentional. Not so many years ago a popular method adopted by those who wanted "to end it all" was to swallow several tablets of bichloride of mercury. Usually this produced the desired result, but in a somewhat unpleasant manner. The study of such cases yielded most of the existing information on acute human poisoning due to inorganic mercury. Other cases of severe or fatal poisoning have occurred following the use of mercuric chloride as a douche, as an antiseptic, and in other medicinal applications. Less serious poisoning was not uncommon when inorganic mercurials were widely used in the treatment of syphilis. Occupational poisoning due to inorganic mercury is usually, but not entirely, of the chronic type.

History

A recent textbook on occupational diseases[1] includes mercury in a chapter entitled "The Ancient Metals." It is true that mercury is one of the earliest recognized industrial poisons and has been surpassed in this respect only by lead. Hippocrates, Pliny the Elder, Galen, and several other writers of antiquity,[2] have mentioned mercury poisoning. The dangerous effects of mercury vapors are discussed at length in a work by Ulrich Ellenbog printed in Germany in 1524, and a detailed clinical description of occupational mercury poisoning was published by Jean Fernel* in France in 1557. These are but a few of the many scientists of early times who have contributed to our knowledge of inorganic mercury and its toxicological effects.[2]

In modern industry, mercury poisoning has commonly been associated with the manufacture of fur-felt hats. Until a satisfactory substitute was found, mercury nitrate was essential to the felting process. The expression "mad as a hatter" is believed to have originated as a result of one of the toxic manifestations of mercury poisoning.

Although a number of the newer industrial applications of mercury involve organic compounds, new uses are constantly being found for metallic mercury, as well as for inorganic mercurials. A very efficient dry-cell electrical battery using both metallic mercury and mercury salts has recently been developed and is in large-scale production. An investment casting process using frozen mercury is gaining acceptance. Mercury salts have been used in paints for ship bottoms to retard the growth of aquatic life. New uses for mercury in the electrical and electronic fields are numerous. It is safe to conclude that occupational mercury poisoning will continue to be a problem for an indefinite period of time and it is difficult to predict when and where it will occur.

---

* Cited in *Occupation and Health*, 1934. International Labour Office, Geneva, Switzerland.

General Considerations

Volatility. Mercury is unique among the heavy metals in that it has considerable volatility at ordinary room temperatures. This means that open containers of mercury, or mercury spilled on floors, constitute an appreciable health hazard. We have read several reports[3-6] of mercury poisoning in laboratories in which evaporation from uncovered vessels or from spilled droplets has played a prominent role. It goes without saying that the rate of vaporization increases with a rise in temperature. The vapor pressure of mercury is given as 0.0007775 mm. at 10° C., but this figure is more than doubled at 20°C., is increased sixfold at 30° C., and twelvefold at 40° C.

Surface area. It is a common observation that spilled mercury tends to become divided into innumerable small globules. This subdivision increases the surface area and consequently increases the rate of evaporation. Thus a ball of mercury one inch in diameter will have a surface area of about 3.1 sq. in. If broken up into spheres $^1/_{32}$ in. in diameter, the total surface area of the resulting globules would be about 100 sq. in.

Routes of absorption. The most important route of absorption for all occupational poisons is through the respiratory tract, and this is true of mercury and its compounds. Mercury, however, is among those substances that can gain access to the living organism through the intact skin, a characteristic that formed the basis for the treatment of syphilis by "mercury inunctions." Cases of mercury poisoning are still encountered in situations where the respiratory hazard has been well-controlled, but where inadequate precautions have been taken against skin absorption. Entry through the gastrointestinal canal is of minor significance in occupational mercurialism, but obviously may be of prime importance if a food or beverage is accidentally contaminated with some form of mercury.

Site and type of action. Mercury may attack one or more of several parts of the body. The gums and nervous system are most commonly involved in occupational poisoning, but the damage is by no means necessarily confined to those two areas. A fuller discussion of this point will be given below under the heading *Toxic Manifestations.* Mercury poisoning may be acute, subacute, or chronic. Generally speaking, industrial poisoning is of the chronic type and nonindustrial is acute. The manifestations of the 2 types may be quite different; incidentally, the symptoms of organic mercury poisoning may be different from those produced by inorganic mercury.

Tolerance. The human organism is able to absorb and excrete substantial amounts of mercury without developing any untoward manifestations. Thus measurable quantities are routinely ingested in the normal diet and otherwise, and amalgam dental fillings also contribute to daily absorption. Humans not exposed to mercury show substantial amounts in their urine, and tissues of nonexposed individuals show mercury in all of the cells.[7, 8, 9]

The kidneys have a definite capacity to eliminate mercury, so that accumulation takes place only when the absorption rate exceeds this capacity.[10] In man it is considered that for concentrations below 1.0 mg. 10 cu. m. of air, elimination is complete; for concentrations greater than 1.0 mg., some Hg is retained temporarily in tissue combinations while, in very high concentrations, for example as high as 10 mg., the characteristics of toxicity and elimination are apt to be quite variable. Of course, it should be pointed out that, in common with most other materials, the effects of mercury vary with different individuals (individual susceptibility or hypersensitivity). It is not rare to find industrially exposed workers who excrete 2 mg. of mercury, or even more, daily without exhibiting any abnormal symptoms or physical signs. Furthermore, the cardinal signs of mercurialism (described below) are easy to detect. Consequently, affected subjects can promptly be removed from further exposure, and corrective measures can be applied to the environment. Even in severe cases of poisoning, the signs and symptoms almost invariably clear up after the exposure has been terminated.

Toxic Manifestations

Acute poisoning. As mentioned above, acute mercury poisoning is rare in industry, but it may occur following the intentional or accidental ingestion of inorganic mercury compounds. According to Sollmann,[11] 100 to 500 gm. of metallic mercury, when taken by mouth, usually pass off in the feces with little toxic effect, but sometimes there may be stomatitis and diarrhea, occasionally severe or fatal poisoning. Mercuric chloride, if swallowed, causes an almost immediate irritative action on the throat and stomach. There is burning of the mouth and bloody vomiting, followed by severe bloody diarrhea. Within a matter of hours there is a suppression of urine that may become complete. Death is usually due to uremia. Post-mortem examination shows inflammation and corrosion along the alimentary canal and severe damage to the kidneys. Glomeruli as well as tubules are involved.

Intense industrial exposure to heated mercury vapors is said to cause pneumonitis and, occasionally, a symptom complex resembling metal-fume fever. Acute skin reactions following contact with mercury compounds have occurred both in industry and as a result of therapeutic applications.

Chronic poisoning. It is this form that is most commonly encountered in industry following exposure to excessive concentrations of mercury vapor, or dust of mercury salts, for periods of weeks, months, or years. The most frequent manifestations are: (1) gingivitis and stomatitis, often associated with loss of teeth; (2) tremor, involving the hands and later other parts of the body; and (3) personality change known as erethism. This condition is characterized by irritability, bursts of temper, and excitability, sometimes alternating with depression. There are numerous other signs and symptoms, including salivation, loss of appetite, weight loss, weakness, and disturbances of urinary and gastrointestinal function.

The laboratory findings in chronic mercurialism are of particular interest, especially the urinary picture. It has been shown that the concentration and amount of mercury in the urine correlate fairly well with the intensity of occupational exposure, but such a relationship is by no means constant.[12] Gibbs[13] has reported that the urinary excretion of mercury in unexposed humans averages about 7.6 μg. per day. Thus the mere qualitative finding of mercury in the urine has little or no diagnostic value. With high occupational exposure the urinary mercury may reach a concentration of 4.0 mg. l. or more.[12] It has been shown with a reasonable degree of certainty that there is little or no correlation between urinary mercury levels and the severity of symptoms.[12, 14] We may therefore conclude that, while urinary mercury levels may give some indication of the degree of exposure, they are of limited value in the diagnosis of poisoning, since high levels can be found in human subjects who are symptom-free, and low levels in those exhibiting marked evidence of mercurialism. It has been suggested that, in some cases, failure to excrete mercury is a factor in the development of poisoning.[12]

There has been some uncertainty as to whether or not occupational poisoning due to inorganic mercury produces laboratory evidence of kidney damage. Two recent reports, however, seem to establish the fact that albuminuria, severe enough to result in a nephrotic syndrome, can occur.[15, 16]

Relatively little has been written concerning blood changes in chronic industrial mercury intoxication. Occasional references are found to "relative lymphocytosis," but this appears to be nothing more than a reflection of the acceptance of misleading normal standards.[17] The occurrence of "mild secondary anemia" among workers exposed to mercury compounds is also mentioned, but no control blood studies were made to support this observation.[18] Sollmann,[11] quoting 2 earlier observers, states that "small doses of mercury raise the blood count." More recent reports suggest that chronic industrial exposure may result in increased hemoglobin values, decreased erythrocyte counts, increased average erythrocyte size, and absolute monocytosis.[14, 17]

Prevention

The prevention of occupational mercury intoxication is based on the same principles that apply to the control of all industrial health hazards. These principles involve measures directed to the working environment and measures directed to the worker. The major features of environmental control are: (1) enclosure or segregation of mercury containers and mercury processes, where possible; (2) adequate general and local ventilation to maintain an atmospheric concentration of mercury well below the so-called threshold limit of 0.1 mg. cu. m. of air; (3) periodic testing of the atmosphere to see that the threshold limit is not exceeded; and (4) scrupulous attention to "housekeeping." The last of these requirements may call for the installation of impervious flooring slanted to a water-trapped catch basin and special covering of all floor-to-wall and floor-to-machinery joints. Spilled mercury that does not run to the catch basin should be picked up immediately with a vacuum line connected to an inertia water trap. Periodic sweeping with flowers of sulfur, calcium polysulfide, or a thiosulfate-type reagent is often desirable. Workbenches on which mercury is handled should have built-up edges to prevent spillage to the floor and should be slanted to a water-sealed collecting vessel.

There are several satisfactory methods of performing quantitative air analyses for mercury. The presence of mercury vapors can be determined by the use of a device that depends on the blackening of selenium sulfide paper. At least 2 instruments available on the market operate on the principle that mercury vapor will absorb light of a certain wave length (2537 A.). By the use of phototubes, a direct reading of mercury-vapor concentration in air can be made. A disadvantage of this method is that other vapors may interfere with the accuracy of the readings. Neither of the above methods is satisfactory for the determination of the concentration of mercury-containing dust in the air. For this, it is necessary to use a dust-sampling device such as the impinger. A method described by Barnes[19] has received wide acceptance.

Preventive measures directed to workers begin with proper selection of those who may be exposed to mercury compounds. Poor teeth, inflamed gums, or poor oral hygiene may be a cause for exclusion. Previous or present renal disease is a contraindication to working with mercury, and it may be desirable to exclude persons having nervous or mental aberrations.

A regular program of periodic medical examinations is an essential part of a preventive regime. Partial examinations, limited to inspection of the mouth, testing for tremor of the hands, and a urinalysis, can easily be done and should be performed at intervals of from 1 to 3 months in most situations. More complete examinations ordinarily need not be undertaken more than once or twice a year. The frequency with which the urinary excretion of mercury is determined depends on the environmental conditions and the findings in the physical examinations. A satisfactory method for evaluating mercury in urine is that of Gettler and Lehman.[20]

Personal hygiene and personal protective measures form an important part of any preventive program. Work uniforms that are changed and laundered frequently, separate lockers for work and street clothing, adequate washing facilities and wash-up time, a suitable eating place free of mercury contamination, all are among the provisions that the employer must make available. The employee must be instructed as to the importance of using these facilities, particularly in relation to reducing the possibility of skin and alimentary tract absorption.

There are several satisfactory respirators that are effective against mercury-containing dust, but only one on the market that, according to its manufacturer, is effective against mercury vapor. This is the Mersorb Cartridge made by the Mine Safety Appliances Company of Pittsburgh, Pa., and used with their chemical cartridge respirator CD-44158. The cartridge should be changed after 2 or 3 days' use.

Treatment of Mercury Poisoning

There is convincing evidence that 2,3-dimercaptopropanol (BAL) is highly effective in the treatment of acute mercury poisoning.[21] It has also been shown that BAL will increase the rate of excretion of mercury in chronic poisoning,[22] but as yet there have been no reports of extensive studies on the effects of this therapeutic agent on the course of chronic industrial mercury intoxication.

References

1. Hunter, D. 1955. The Diseases of Occupations. Little, Brown & Co. Boston, Mass.
2. Goldwater, L. J. 1936. From Hippocrates to Ramazzini: early history of industrial medicine. Ann. med. Hist. **8:** 27.
3. McCarroll, C. F. 1939. Hazards of mercury vapor in analytical petroleum laboratories. Rept. Invest. 3475. U. S. Bur. Mines. : 13–15.
4. Shepard, M., S. Schuhmann, R. Flinn, J. W. Hough & P. A. Neal. 1941. Hazards of mercury vapor in scientific laboratories. Research Paper 1383. U. S. Natl. Bur. Standards. : 357–375.
5. Beauchamp, I. L. & B. D. Tebbens. 1951. Mercury vapor hazards in the university laboratories. Am. Ind. Hyg. Assoc. Quart. **12:** 171.
6. Goldwater, L. J., M. Kleinfeld & A. R. Berger. 1956. Mercury exposure in a university laboratory. Arch. Ind. Health. **13:** 245.
7. Szép, Ö. 1940. Weitere Beiträge zur Kenntnis des Quecksilbergehalts des menschlichen Körpers. Biochem. Z. **307:** 79.
8. Gibbs, O. S. 1941. Toxicological studies on ammoniated mercury. J. Pharmacol. Exptl. Therap. **72:** 16.
9. Forney, R. B. & R. N. Harger. 1949. Mercury content of human tissues from routine autopsy material. Federation Proc. **8:** 292.
10. Ashe, W. F. 1953. Behavior of mercury in the animal organism following inhalation. Arch. Ind. Hyg. and Occupational Med. **7**(1): 19.
11. Sollmann, T. 1949. A Manual of Pharmacology. 7th ed. W. B. Saunders. Philadelphia, Pa.
12. Smith, A. R.& S. Moskowitz. 1948. Urinary excretion of mercury. Monthly Review. N. Y. State Dept. of Labor Div. Indust. Hyg. & Safety Standards. **27:** 45.
13. Gibbs, O. S. Cited by Sollmann in reference No. 11.
14. Shoib, M. O., L. J. Goldwater & M. Sass. 1949. A study of mercury exposure. Am. Ind. Hyg. Assoc. Quart. **10:** 2.
15. Friberg, L. & S. Hammarström. 1953. Kidney injury after chronic exposure to inorganic mercury. Arch. Ind. Hyg. and Occupational Med. **8:** 149.
16. Goldwater, L. J. 1953. Kidney injury after chronic exposure to inorganic mercury. Arch. Ind. Hyg. and Occupational Med. **8:** 588.
17. Goldwater, L. J. 1947. Physiology of the bone marrow in relation to industrial intoxication. Occupational Med. **4:** 435.
18. Neal, P. A. *et al.* 1937. A study of chronic mercurialism in the hatters' fur-cutting industry. U. S. Public Health Service. Public Health Bull. No. 234.
19. Barnes, E. C. 1946. Determining the concentration of mercury in air. Am. Ind. Hyg. Assoc. Quart. **7:** 26.
20. Gettler, A. O. & R. A. Lehman. 1938. A simplified procedure for the determination of mercury in urine. Am. J. Clin. Pathol. **8:** 161.
21. Longcope, W. T. & J. A. Luetscher, Jr. 1946. The treatment of acute mercury poisoning by B.A.L. J. Clin. Invest. **25:** 557.
22. Bell, R. F., J. C. Gilliland & W. S. Dunn. 1955. Urinary mercury and lead excretion in a case of mercurialism. Arch. Ind. Health. **11:** 231–233.

THE PHARMACOLOGY OF MERCURY AND ITS COMPOUNDS

By Harold A. Shoemaker
University of Oklahoma School of Medicine, Oklahoma City, Okla.

The use of mercury and its compounds in industry and medicine began in antiquity, but its pharmacological effects are still not fully understood. Despite the obvious utility of the compounds used in the past, their toxicity overshadowed their usefulness.

The later rediscovery of the diuretic effect of mercurous chloride by Wood[1] in 1849 and by Jendrassick[2] in 1886 contributed to the development of the usefulness of mercurials in the treatment of edematous states, but it was the discovery,[3a] in 1920, of the diuretic effect of an organic compound of mercury (Novasurol) that initiated a new phase in therapeutics and gradually led to the development of the organomercurial diuretics, now regarded as "the most reliable diuretic agents and the most powerful."[3b]

The introduction of the new organomercurial compounds calls for pharmacological differentiation among the actions of metallic mercury, of the inorganic salts, of the older organic compounds, and of the newer organomercurials.

Problems in the Pharmacology of Mercury

The problems of the pharmacology of mercury are inherent in the nature of the mercury compounds themselves and in the techniques available for study.

(1) Mercury in different forms reacts differently with various tissues. Mercury and its compounds have an affinity for the thiol groups found in proteins and in enzyme systems, but the exact composition of the complexes formed with sulfhydryl-containing substances in the body is not known. The older mercurials precipitated tissue proteins, and later ones were irritating to tissue, but these properties are not possessed by the newer organomercurials.

The pharmacological effects of different forms of mercury (inhaled metallic mercury, ingested bichloride of mercury, and orally or parenterally administered organomercurial complexes) all differ from one another. As Goodman and Gilman[4] point out in the new edition of their textbook: "Older evidence suggests that the organic mercurials were active by virtue of their release of the mercuric ion (Hg^{++}). However, it is more likely that organic mercury complexes dissociate as such and act in the form of $R-Hg^{+}$." The recent work of Weiner and Müller[5] suggests that the form may be $R-Hg=R'$, where the R' is a cysteine-like complex.

(2) The combination of mercury with proteins is not a simple one-way chemical reaction, but a two-way equilibrium. For example, if a solution of bichloride of mercury is dropped into a solution of egg albumin, a precipitate of mercury albuminate forms at the point of contact. When the test tube is shaken so that an excess of albumin comes in contact with the precipitate, this precipitate is redissolved. The organomercurial compounds, as Pitts and Sartorius[6] have pointed out, fail to precipitate tissue proteins because a large excess of protein at the repository site prevents precipitation.

(3) Mercury reactions are sensitive to *p*H; therefore, any studies of the fate and excretion of mercury must take into account the *p*H of the patient's blood and tissues.[6] Differences in *p*H may explain in part the apparent variations in the results of various studies on mercury excretion.

(4) Mercury and its compounds are volatile substances, a fact that has been emphasized by Kelly *et al.*[7] and by Burch *et al.*[8] but that has been ignored by other observers, whose difficulty in accounting for all of the ingested or parenterally administered mercury may be due in part to the loss of mercury in the breath and from the surface of the skin, or to volatilization from laboratory specimens.

(5) When studying the fate and excretion of mercury, it is important to consider the fact that almost all of the ingested mercury is excreted very rapidly and that only clinically insignificant traces remain somewhat longer in the body. Sollmann[9] and others[8, 10] have pointed out that, in the absence of severe and pre-existing renal impairment, excretion is almost complete the first day and absolutely so within the first week.

This rapid excretion is important both experimentally and clinically. In tissue studies, it is necessary to ascertain when the patient last received mercury. If the last administration has been very recent, some mercury may still be in transport and on its way out of the body through the kidney. Greenblatt[11] has recently made this same point.

From the pathological point of view, however, these time relationships are not important. It has been shown by Griffith[12] and others[13, 14] that the traces of mercury found in various tissues have no correlation with the pathology.

(6) Finally, let us remember that with any substance, *dosis sola venenum facit* (the dose alone determines the poison).[15] Mercury, in detectable amounts, is present in the food we eat and in the air we breathe, and it is normally present in all tissues of all persons.[16, 17, 18]

Absorption

Mercury and its compounds are absorbed from all surfaces of the body. The rate of absorption, as with all substances, depends upon the form in which mercury is presented, the solubility of the preparation, the degree of dispersion, and the absorbing surface. Metallic mercury and mercurous chloride, when applied by inunction, are in a state of fine division, and are absorbed through the skin.[18a] Inhalation of mercury vapor or of mercury-containing powder (for example, the combination of mercury and chalk used in developing latent fingerprints) has resulted in many cases of mercury intoxication.[19, 20, 21]

All compounds of mercury, when injected, are absorbed from tissue spaces. The soluble inorganic salts of mercury are absorbed from the alimentary canal. The more soluble compounds are the most rapidly absorbed. The mercury from these inorganic salts readily reacts with albumin to form a soluble mercury albuminate.[9]

From studies on the organic mercurial compounds, Hunt and his co-workers[22] concluded that a weakly acid heterocyclic compound, such as theophylline or succinimide, enhances the rate of absorption of nondiuretic as well as diuretic compounds. In clinical studies DeGraff and his colleagues[23] found a marked increase in diuretic efficiency when theophylline was added to the mercurial diuretic. They concluded that the superiority of the combination was due in part to the increased absorption and diminished local reaction.

The absorption of organomercurials from the gastrointestinal tract apparently depends on the composition of the compound under test. Huffman[24] found that when a mercurial diuretic (Mercuhydrin) was administered by mouth, absorption was relatively poor, as indicated by the small percentage of the administered dose excreted in the urine. Vogl[25] has reported that, with some mercury compounds, 5 to 10 per cent of the ingested mercury was absorbed and then excreted in the urine. He stated that Neohydrin, for example, was effective in doses containing the equivalent of 40 to 48 mg. mercury, but that other compounds required a dosage corresponding to 75 to 180 mg. mercury per day.

In their bioassay studies of oral diuretics, Greiner and his colleagues[26] showed that Mercuhydrin, when given orally, was about one twenty-fourth as potent as when administered intramuscularly. Neohydrin was found to have an intramuscular-to-oral potency ratio of 4 to 1, significantly greater than that for the other compounds they studied. Their work indicates that clinically effective absorption takes place, since 6 tablets of Neohydrin (the equivalent of 60.0 mg. mercury) have a diuretic effect comparable to 1.1 cc. injected Mercuhydrin (the equivalent of 43.8 mg. mercury).

Fate and Excretion

Mercury, regardless of the route of administration or the type of compound, is excreted by all channels: urine, feces, sweat, milk, and so on. The two main channels are the urine and feces, of which the urine is the more important.

Sollmann,[9] has published a classic treatment of the subject based on the older work with mercury and its compounds. He used the simpler soluble and insoluble, organic and inorganic preparations available at that time. Most of the soluble compounds used were highly ionizable. Taking into consideration the type of compound and the rate and route of administration, he classified the urinary excretion into three categories: (1) continuous, progressively increasing excretion (with relatively insoluble compounds, such as calomel or metallic mercury); (2) "incompletely remittent cumulative excretion" (with more soluble compounds, such as mercuric salicylate); and (3) a periodic and completely remittent type of excretion (following all intravenous injections and the intramuscular administration of the nonprecipitating type of organic compounds). In the last category, the rate of excretion rises and declines rapidly, reaching a maximum in 1 to 2 hours, and excretion is almost complete in 8 to 12 hours. This is characteristic of the organomercurials.

Urinary excretion. Vogl[25] has stated that "frequently, however, only 40 to 60 per cent of the mercury is eliminated in the urine during the first day, and 3 to 8 days may elapse before all of the mercury is excreted." Pitts and Sartorius,[6] however, cited 5 studies indicating from 60 to 100 per cent excretion of a therapeutic dose in 24 hours. Handley *et al.*[27] recovered as much as 90 per cent of meralluride in the form of the organic complex in 9 hours and, usually, 99 per cent by the end of the first day.

The presence of theophylline in organic compounds influences the urinary excretion of mercury. DeGraff and his colleagues[28] found that theophylline increased the excretion by from 30 to 40 per cent within 6 hours when Mercurin or Salyrgan was injected intravenously, and by from 100 to 300 per cent after intramuscular injection.

Burch and his co-workers[8] found that one half of the mercury in a radiomercury-labeled diuretic (Mercuhydrin) was excreted in approximately 1 to 8 hours, with a mean value of 3 hours. They found that renal impairment caused a slower rate of excretion. This work has sometimes been cited as prejudicial to the use of mercurials in congestive heart failure; if the summary alone is read, it might be so interpreted. Closer study of this work indicates, however, that the mercury was excreted more slowly than usual only when there was some renal impairment or no diuretic effect. Obviously, in such cases these drugs should be used with great caution. Sound management involves individualized treatment both as to dose and interval.

The exact chemical composition of the excretory products of mercury in the urine is unknown. There is evidence that organomercurial compounds, which have a strong C-to-Hg bond and do not ionize, are excreted in unchanged form.[29] According to Möller,[30] Salyrgan appears in the urine as Salyrgan acid (FIGURE 1), which is kept in solution by the sodium chloride present. Weiner and Müller[5] have presented evidence that mersalyl and chlormerodrin are stable in the body and are excreted quantitatively in the urine as a cysteinelike sulfhydryl complex, and that little, if any, mercury appears in the urine in any other form during the first 3 hours after administration. Handley and his co-workers,[27] using a partition chromatographic method, found that almost all of the Mercuhydrin was excreted as the organic compound.

Fecal excretion. The parenterally administered compounds are excreted into the gastrointestinal tract by the gastric and intestinal secretions and the bile. Lieb and Goodwin[31] found that mercury was excreted via the gastric mucous membrane. Möller,[32] using rabbits, found that the excretion of mercury in 24 hours after an intravenously injected dose of Salyrgan was as follows: 70 to 80 per cent in the urine and 4.5 to 5.0 per cent in the feces. He estimated that approximately one fifth of the fecally excreted mercury entered through the intestinal wall and that the balance was excreted by the liver in the bile.

The excretion of mercury in the milk has also come under consideration, but is now of little practical importance. Legales and Duperoy[33] stated that mer-

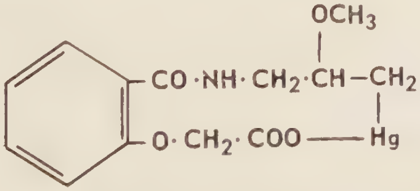


FIGURE 1. Salyrgan acid.

cury could be found in the milk of women who were being treated with mercury, and that the amounts were sufficient to be of importance in the treatment of congenital syphilis. Reed[34] gave a number of references confirming the fact that mercury could be excreted in the milk, but only after considerable delay.

Lomholt[34a] stated that only minute quantities of mercury were found in sweat and saliva. Greenblatt,[11] in preliminary work on 2 humans receiving mercurial diuretics orally, has obtained evidence leading him to believe that some mercury may be lost in the breath.

Effects on the Nervous System

Mercury compounds usually used in therapeutics do not affect the nervous system. However, with some other compounds, toxic effects thereon may be observed because these substances are lipotropic and have a special affinity for the nervous system. In cases of poisoning from the lipotropic organic compounds large amounts of mercury are found in the brain. Considerable damage to the nervous system was observed microscopically by Hunter and his colleagues[35] when they administered methyl mercury iodide and nitrate to animals. The organomercurial diuretics do not appear to be lipotropic. Müller[36] did not find any mercury in the brain of a dog that was sacrificed 2 hours after a large intravenous dose of Salyrgan.

Cardiac Effects

The cardiac effects of mercury compounds are of particular interest to the clinician who administers such diuretics intravenously. A number of reports in the older literature deal with cardiac damage from intravenously administered mercurial diuretics, but it is difficult to evaluate these reports since no precise information as to rate of administration was given. Purine derivatives, when used in conjunction with the mercurial diuretics, decrease their toxicity to the heart.

On the basis of both pharmacological and clinical evidence, the cardiac effects of the mercurial compounds should not militate against the use of these drugs. These toxic effects are observed only on intravenous administration and then only when the rate of injection is so rapid that a high concentration comes into contact with the cardiac muscle. There are no reports of this effect when mercurial diuretics are given in the regular dosage and by routes other than the intravenous.

Conclusions

Despite the long history of mercury and its compounds, many pharmacological questions remain for future research to resolve. Recent evidence does indicate, however, that generalized statements—amounting almost to prejudices—concerning the effects of mercury compounds are not warranted by the facts presently available. Each group of mercury compounds has its own characteristics, which often are more closely related to the properties of the rest of the molecule than they are to any supposed generic qualities of mercury itself. A new and challenging phase in the pharmacology of mercury has been opened with the development of the new organomercurials, which appear to have properties quite distinct from those of the ionizable salts that yield free mercury ions when they dissociate. As with most other substances, the form and quantity in which mercury compounds are administered determine their pharmacological activity. This knowledge is hardly new for, in the 10th century, an Arab physician, Rhases, administered a substantial quantity of mercury orally to an ape, who "suffered only a belly ache."[37]

References

1. Griffith, J. P. C. & H. W. Cattell. 1890. Sajous' Ann. Univ. Med. Sci. **5:** A-56.
2. Jendrassick, E. 1886. Kalomel als Diuretikum. Deut. Arch klin. Med. **38:** 499.
3a. Saxl, P. & R. Heilig. 1920. Über die diuretische Wirkung von Novasurol und anderen Quecksilber-präparaten. Wien. klin. Wochschr. **33:** 943.
3b. Handley, C. A. 1954. Diuretics. *In* V. A. Drill. Pharmacology in Medicine. McGraw-Hill. New York, N. Y.
4. Goodman, L. & A. Gilman. 1955. The Pharmacological Basis of Therapeutics. 2nd ed. Macmillan. New York, N. Y.
5. Weiner, I. M. & O. H. Müller. 1955. A polarographic study of Mersalyl (Salyrgan)-thiol complexes and of the excreted products of Mersalyl. J. Pharmacol. Exptl. Therap. **113:** 241.
6. Pitts, R. F. & O. W. Sartorius. 1950. Mechanism of action and therapeutic use of diuretics. Pharmacol. Revs. **2:** 195.
7. Kelly, F. J., C. T. Ray, S. A. Threefoot & G. E. Burch. 1950. The influence of self-absorption, volatilization and deliquescence in counting of radioelements. J. Lab. Clin. Med. **35:** 606.
8. Burch, G., T. Ray, S. Threefoot, F. J. Kelly & A. Svedberg. 1950. The urinary excretion and biological decay period of radiomercury labelling a mercurial diuretic in normal and diseased man. J. Clin. Invest. **29:** 1131.
9. Sollmann, T. 1948. A Manual of Pharmacology. 7th ed. W. B. Saunders. Philadelphia, Pa.
10. Sollmann, T., N. E. Schreiber & H. N. Cole. 1935. Excretion of mercury after clinical intramuscular and intravenous injections. Arch. Dermatol. and Syphilol. **32:** 1.
11. Greenblatt, I. J. 1956. Personal communication.
12. Griffith, G. C., E. M. Butt & J. Walker. 1954. The inorganic element content of certain human tissues. Ann. Internal Med. **41:** 501.
13. Borinski, P. 1931. Sind kleinste Quecksilbermengen gesundheitschädlich? Deut. med. Wochschr. **25:** 1060.
14. Stock, A. 1943. Der Quecksilbergehalt des menschlichen Organismus. II. XXXIII. Mitteilung: Über Wirkung und Verbreitung des Quecksilbers. Biochem. Z. **316:** 108.
15. Macht, D. I. 1938. A drug or poison? Sci. Monthly. **47 :** 34.
16. Szép, Ö. 1940. Weitere Beiträge zur Kenntnis des Quecksilbergehalts des menschlichen Körpers. Biochem. Z. **307:** 79.
17. Gibbs, O. S. 1941. Toxicological studies on ammoniated mercury. J. Pharmacol. Exptl. Therap. **72:** 16.
18. Forney, R. B. & R. N. Harger. 1949. Mercury content of human tissues from routine autopsy material. Federation Proc. **8:** 292.
18a. Schamberg, J. F. 1918. Experimental study of mode of absorption of mercury when applied to the skin. J. Am. Med. Assoc. **70:** 142.
19. Bidstrup, P. L. 1951. Chronic mercury poisoning in men repairing direct current meters. Lancet. **2:** 856.
20. Agate, J. M. & M. Buckell. 1949. Mercury poisoning from fingerprint photography. Lancet. **2:** 451.
21. Blench, T. H. & H. Brindle. 1951. Fingerprint detection and mercury poisoning. Lancet. **1:** 378.
22. Hunt, W. H., L. A. Walter & R. J. Fosbinder. 1942. Organic mercurials: The influence of structure on absorption and excretion. J. Am. Pharm. Assoc. Sci. Ed. **31:** 278.
23. DeGraff, A. C., R. C. Batterman & R. A. Lehman. 1938. The influence of theophylline upon the absorption of mercupurin and salyrgan from the site of intramuscular injection. J. Pharmacol. Exptl. Therap. **62:** 26.

24. Huffman, E. R. 1949. Mercury excretion following oral mercurial diuretics in man. Am. J. Med. **6:** 663.
25. Vogl, A. 1955. The use of mercurial diuretics in congestive heart failure. Modern Concepts of Cardiovascular Disease. **24:** 263.
26. Greiner, T., H. Gold, F. Palumbo, L. Warshaw, J. Weaver, R. Marsh, S. Marties & M. T. Kevit. 1952. Human assay of three new mercurial diuretic agents: a promising preparation for oral use. Proc. Soc. Exptl. Biol. Med. **80:** 117.
27. Handley, C. A., J. H. Moyer & R. A. Seibert. 1955. The urinary excretory products after meralluride administration. American Heart Assoc. Exhibit. New Orleans, La.
28. DeGraff, A. C., R. C. Batterman, R. A. Lehman & E. Yasuna. 1938. Excretion of mercury following administration of mercurial diuretics with and without theophylline. Proc. Soc. Exptl. Biol. Med. **39:** 250.
29. Handley, C. A. Personal communication.
30. Möller, K. O. 1930. Experimentelle Untersuchungen über die Pharmakologie des Salyrgans. IV. Mitteilung: Untersuchungen über die Chemie des Salyrgans. Arch. exptl. Pathol. Pharmakol. **153:** 109.
31. Lieb, C. C. & G. M. Goodwin. 1915. The excretion of mercury by the gastric mucous membrane. J. Am. Med. Assoc. **64:** 2041.
32. Möller, K. O. 1930. Experimentelle Untersuchungen über die Pharmakologie des Salyrgans. V. Mitteilung: Das Verhalten des Quecksilbers im Organismus nach Verabfolgung von Salyrgan. Fortgesetzte Untersuchungen über die Salyrgannephritis bei Kaninchen. Arch. exptl. Pathol. Pharmakol. **154:** 236.
33. Legales & Duperoy. 1900. Trans. XIII. Intern. Congr. Med. Paris. Quoted by Russell van Arsdale Lee. 1923. The pharmacology of mercury. J. Am. Med. Assoc. **81:** 1748.
34. Reed, C. B. 1908. A study of the conditions that require the removal of the child from the breast. Surg. Gynecol. Obstet. **6:** 514.

34a. Lomholt, S. 1920. Absorption and elimination of mercury in the different methods used in the treatment of syphilis. Brit. J. Dermatol. Syphilis. **32:** 353.

35. Hunter, D., R. R. Bomford & D. S. Russell. 1940. Poisoning by methyl mercury compounds. Quart. J. Med. **9:** 193.
36. Müller, J. 1928. Tierexperimentelle Untersuchungen über die Verteilung des Quecksilbers im Organismus und klinische Erfahrungen über die Ausscheidung desselben nach Salyrganinjektionen. Arch. exptl. Pathol. Pharmakol. **114:** 1.
37. Mettler, C. C. 1947. History of Medicine. Blakiston. Philadelphia, Pa.

AN ANALYSIS OF THE EXCRETORY PRODUCTS OF A MERCURIAL DIURETIC (MERALLURIDE) BY COLUMN CHROMATOGRAPHY

By John H. Moyer, Carroll A. Handley, and Richard A. Seibert
Department of Pharmacology, Baylor University College of Medicine, Houston, Texas

One concept of the diuretic action of the organomercurial compounds is based on the release of inorganic mercury, which is presumed to be responsible for reversibly inhibiting the sodium chloride reabsorbing mechanism of the renal tubules. Pertinent information concerning the excretory products of mercurial diuretics can be obtained by the aid of adsorption chromatography.[1] Since meralluride (Mercuhydrin) is the sodium salt of a carboxylic acid, an anionic adsorbent will retain the compound selectively, whereas the decarboxylated residue or released inorganic mercury will pass through the column.[1] Acid aluminum hydroxide was used as the adsorbent. The excretory products of meralluride were studied on dogs in the laboratory, on normal control human subjects, and on patients with heart failure.

Methods and Materials

Chemical procedure. Acid aluminum hydroxide (Woelm) was selected as the adsorbent. A column 1.2 × 19 cm. was packed with approximately 5 gm. of the adsorbent. In order to test the method, 10 ml. of solution containing known amounts of meralluride and mercuric chloride were passed through the column, followed by 20 ml. of distilled water. The adsorbed fraction was then eluted by passing 10 ml. of 5 per cent sodium carbonate through the column. A 20-ml. aliquot of each fraction was digested with concentrated sulfuric acid made up to 100 ml., and the mercury was determined by a slightly modified method of that employed by Laug and Nelson.[2] The rate of recovery was better than 95 per cent from 10 ml. of solutions containing 1 to 10 mg. of mercuric chloride per 100 ml. and 3 to 80 mg. of meralluride mercury per 100 ml. It was found, likewise, that standard solutions containing known amounts of meralluride and chlormerodrin could be separated quantitatively.

Laboratory observations on excretory products of meralluride. Meralluride was administered to 8 female dogs anesthetized with 30 mg. kg. of pentobarbital in a dosage of approximately 3.9 mg. of meralluride mercury per kg. This dose uniformly produces excellent diuresis.[3, 4] The animals were not hydrated prior to the experiment. Urine samples were collected at intervals of 1 to 2 hours for 8 hours, using indwelling catheters, and 5 to 10 ml. aliquots were chromatographed as outlined above. Ten ml. of the original urine and 20 ml. of each of the 2 fractions from the chromatography column were digested and analyzed for mercury content.

Clinical observations on excretory products of meralluride. Two ml. of meralluride, equivalent to 78 mg. of Hg, were given to 5 normal control subjects by 3 different routes of administration; that is, intravenously, subcutaneously, and intramuscularly. Urine samples were collected for the next 24 hours at

6 hour-intervals. Each 6-hour fraction was analyzed separately for the total excretion of mercury. Aliquots from each urine-collection period also were passed through the chromatography column as outlined above, and they were then analyzed for mercury content as was done with the dog urine.

Six patients with heart failure were treated similarly; 2 of these had been found previously to be unresponsive to mercurial diuretics. These patients received 2 ml. of meralluride intravenously and intramuscularly. The urine was collected over a 24-hour period at 6-hour intervals.

Results

TABLE 1 shows that inorganic mercury could be separated quantitatively from meralluride within the limits of the accuracy of the method (±5 per cent). Fraction *A* (not adsorbed by the column) represents inorganic mercury, whereas fraction *B* (adsorbed by column) represents meralluride mercury.

Laboratory observations on excretory products of meralluride. FIGURE 1 summarizes the recovery rate of mercury from the 2 fractions in 8 dogs. Within 1 hour, an average of 40 per cent of the injected mercury was excreted in the urine and, by 3 hours, approximately 70 per cent was voided. Less than 10

TABLE 1

SEPARATION OF INORGANIC HG AND NONCARBOXYLIC ORGANOMERCURIALS FROM MERALLURIDE AND MERCAPTOMERIN HG BY COLUMN CHROMATOGRAPHY

	Fraction *A*	Fraction *E*
0.325 mg. Meralluride Hg 0.100 mg. Hg as $HgCl_2$	0.104 mg.	0.319 mg.
7.9 mg. Meralluride Hg 1.0 mg. Hg as $HgCl_2$	0.98 mg.	7.95 mg.
4.0 mg. Chlormerodrin Hg 3.9 mg. Meralluride Hg	4.15 mg.	4.16 mg.
4.0 mg. Diglucomethoxane Hg 3.9 mg. Meralluride Hg	4.05 mg.	3.84 mg.
	Fraction *A*	Fraction *B*
4.0 mg. Mercaptomerin Hg 4.0 mg. Chlormerodrin Hg	4.15 mg.	4.05 mg.
4.0 mg. Mercaptomerin Hg 1.0 mg. Hg as $HgCl_2$	0.94 mg.	3.92 mg.

Fraction *A* is the fraction of mercury not retained by the column, and Fraction *E* is the fraction eluted by Na_2CO_3.

per cent was excreted as the unadsorbed fraction. Six hours after the administration of meralluride, an average of 87 per cent of the mercury had been recovered as the adsorbed fraction, whereas less than 10 per cent passed through the column (degradation product). This indicated that the adsorbed fraction was the only component of major significance that was excreted in the urine within the first 6 hours.

Clinical observations on the excretory products of meralluride. When meralluride was given to normal human subjects (FIGURE 2), it was obvious that there was no significant difference in the rate of excretion of mercury after 24 hours with any of the 3 different routes of administration. During the first 6 hours, however, the rate of excretion was slightly more rapid following intravenous administration than when the compound was given subcutaneously or intramuscularly. About 60 to 70 per cent of the mercury was excreted as the adsorbed fraction within the first 6 hours. At the end of 12 hours, 75 to 80 per cent of the mercury was excreted by the different routes. During the next 12 hours very little additional mercury was excreted in the urine. Less than 5 per cent of the mercury was excreted as a degradation product during the 24-hour period following administration. This amount was too small to account for any of the diuresis.

FIGURE 3 compares the excretory rate of mercury as the adsorbed fraction to the excretion rate of sodium during successive 6-hour periods. There was a close parallel between the 2 rates. The maximum increase in the excretion of sodium occurred during the period of maximum urinary excretion of mercury.

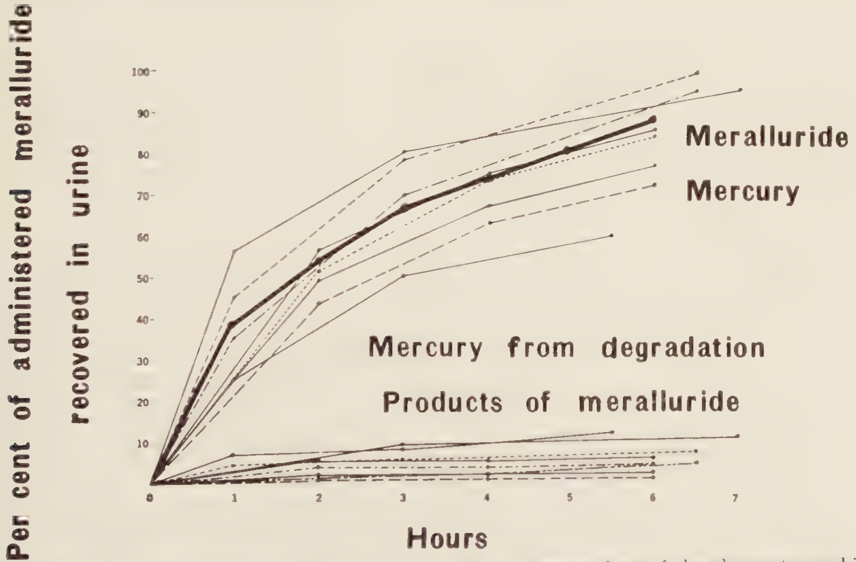


FIGURE 1. Urinary mercury excretion in 8 dogs. A comparison of the chromatographically adsorbed fraction (meralluride mercury) with the nonadsorbed fraction (degradation products). All values for the excretion rates are expressed as percentages of meralluride mercury administered.

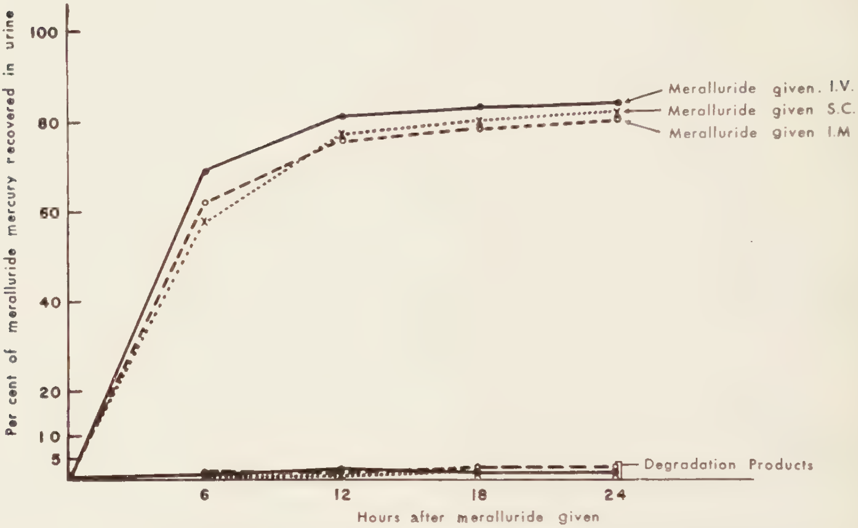


FIGURE 2. Urinary excretion rates of meralluride mercury in normal human subjects. A comparison of the chromatographically adsorbed fraction (meralluride mercury) with the nonadsorbed fraction (degradation products). The rates of excretion following administration by 3 different routes are compared. All values are expressed as percentages of meralluride mercury administered.

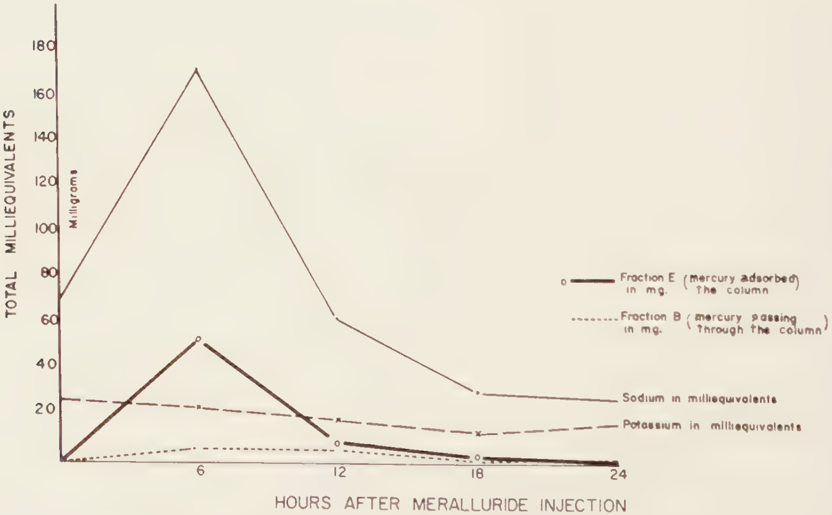


FIGURE 3. Total milliequivalents of sodium and potassium and milligrams of mercury excreted in the urine after the intravenous injection of 2 c.c. of meralluride (78 mg. Hg). The rate of urinary excretion of sodium during successive 6 hour intervals after the administration of meralluride is compared to control values. The rate of excretion of mercury is also plotted for the same successive 6-hour intervals.

There was very little effect on the excretion of potassium throughout the studies.

In summary, it was found that in normal control subjects the mercury was excreted in a form quite similar to that of the injected meralluride when examined by adsorption chromatography. More than half of the mercury administered was excreted during the first 6 hours as the adsorbed fraction, whereas less than 5 per cent was excreted as the degradation products of meralluride. The first 6-hour period was also the period of maximum sodium and water diuresis, and the curves of mercury excretion and sodium excretion paralleled each other very closely. The small fraction not adsorbed by the column seemed to be insufficient to account for the diuresis and natriuresis.

By comparison to normal control subjects, the patients with heart failure tended to excrete mercury more slowly (average values), particularly during the first 12 hours after meralluride administration by the intramuscular route (FIGURE 5). By the end of 24 hours, the excretory rate following intravenous administration was approximately the same in the patients with heart failure as in the normal control subjects (FIGURE 5). Following intramuscular administration, however, the excretory rate of the adsorbed fraction was only 65 per cent for the group as compared to approximately 82 per cent following intravenous administration (FIGURE 4). Here, too, the amount of mercury excreted as degradation products of meralluride was insignificant for the group, being less than 10 per cent of the total urinary excretion of mercury.

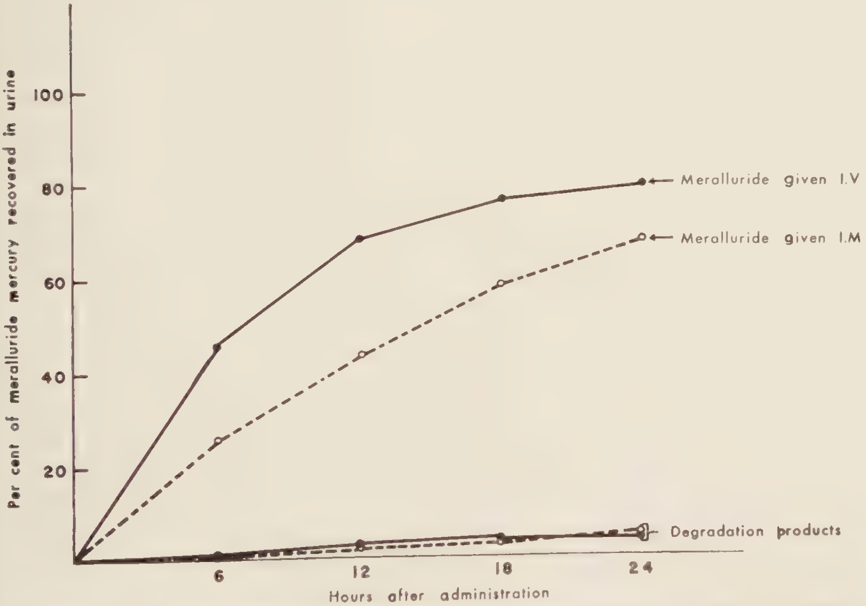


FIGURE 4. Urinary excretion rates of meralluride mercury in patients with heart failure. A comparison of the chromatographically adsorbed fraction with the nonadsorbed fraction. The rates of excretion following administration by the intravenous and intramuscular routes are compared. Values are expressed as percentages of meralluride mercury administered.

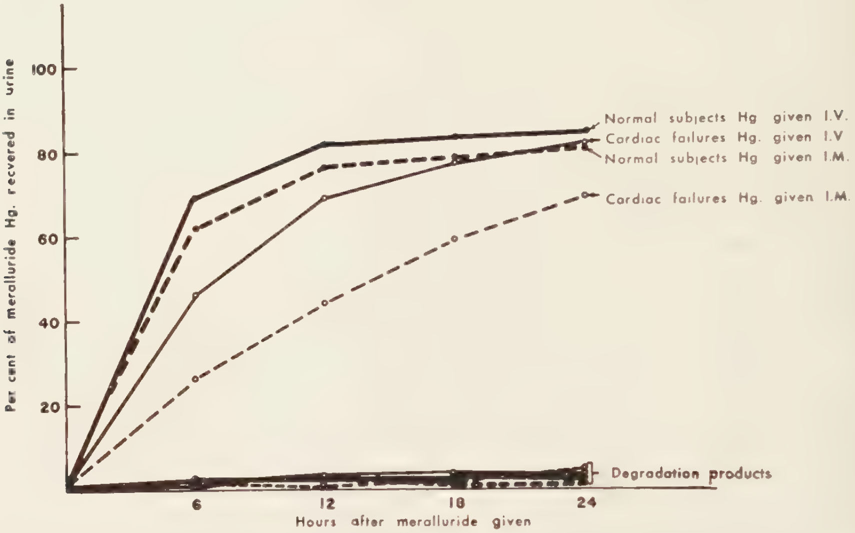


FIGURE 5. Comparison of the rates of excretion of meralluride mercury given intravenously and intramuscularly in a control subject and in patients in heart failure.

When the patients with severe heart failure, who were unresponsive to mercurial diuretics, were compared with those who were responsive, a difference in excretory rate of mercury was evident. For example, in FIGURE 6 a patient who was responsive to meralluride administration was compared with one who was unresponsive. In the patient who responded, 86 per cent of the meralluride mercury was excreted within 18 hours following intravenous administration and about 72 per cent following intramuscular administration. Less than 5 per cent was excreted as degradation products. In the unresponsive patient, however, only 60 per cent of the mercury was excreted as meralluride mercury 24 hours after intravenous administration. Following intramuscular administration, during the first 12 hours less than 10 per cent was excreted as meralluride mercury; only 35 per cent was voided by the end of 18 hours; and 46 per cent was excreted after 24 hours. Interestingly enough, in this patient, who was unresponsive to meralluride and retained the meralluride for a fairly long period of time before excretion, the degradation products increased significantly. After intramuscular administration more than 20 per cent of the mercury passed through the column (the nonadsorbed fraction). This suggests that the retention of meralluride within the body results in significant degradation of the organomercurial. FIGURE 7 compares the over-all excretory rates of mercury for the responsive patients with those of the nonresponsive patients. These observations only further confirm those made on the individual patients noted in FIGURE 6.

As in the normal control subjects, the increase in the excretion rate of sodium in patients with heart failure closely paralleled the excretory rate of the mercury (adsorbed fraction). For example, following intravenous administration,

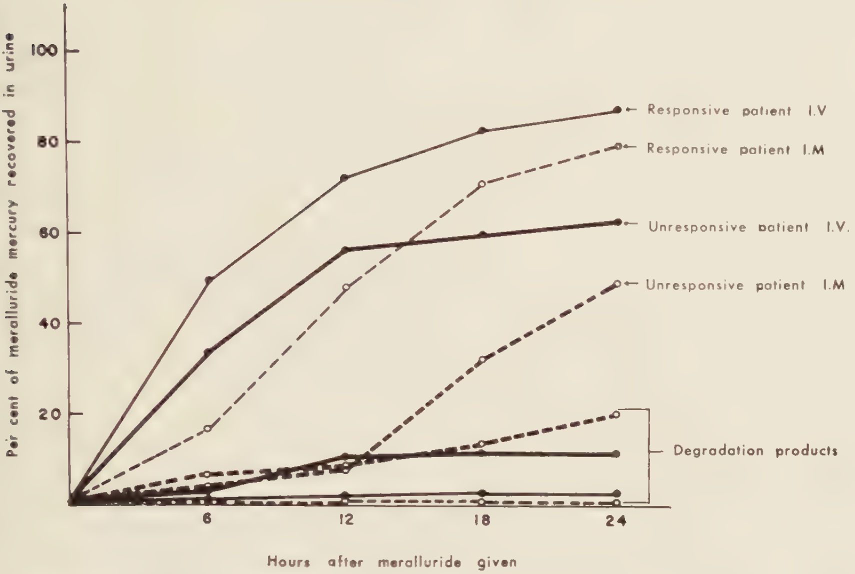


FIGURE 6. Urinary excretion rates of mercury in 2 patients with heart failure. One was responsive to meralluride; the other was not. The values for both the adsorbed fraction (meralluride mercury) and the nonadsorbed fraction (degradation products) are expressed in percentages of meralluride mercury administered.

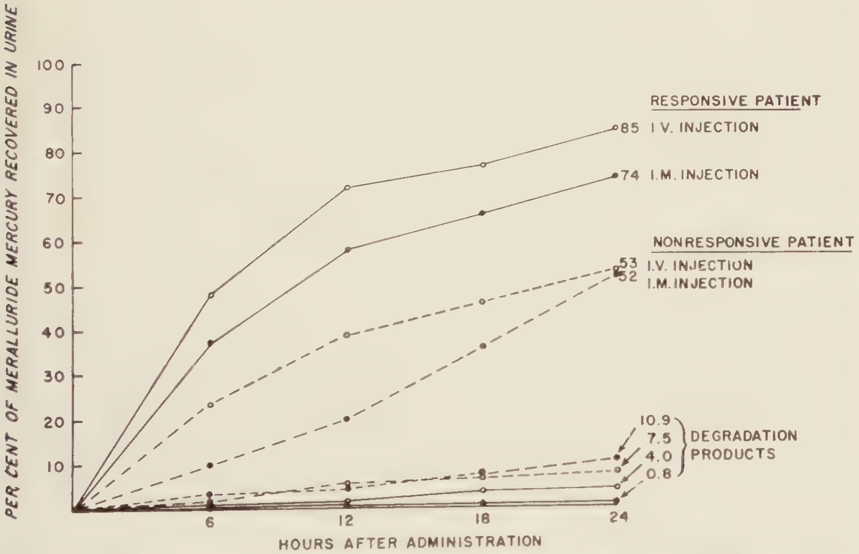


FIGURE 7. Comparison of urinary mercury excretion (average values) in 5 patients who diuresed following the administration of meralluride with that in 2 patients who did not respond. The values are expressed in percentages of meralluride mercury administered. The dosage was 78 mg. meralluride mercury.

the sodium-excretion rate increased from 11 to 67 milliequivalents (mEq.) within 6 hours and remained at 29 mEq. during the next 6-hour interval. After 18 hours, however, the excretion rate returned to the control value. Following intramuscular administration, the excretion rate of sodium increased from 20 to 30 mEq. after 6 hours and remained at 25 mEq. during the next 6 hours, following which the excretion rate returned to the control level.

Discussion

The results show that inorganic mercury and noncarboxylic organic mercury compounds can be separated quantitatively from meralluride, a carboxylic-acid compound, by adsorption chromatography. Meralluride is very firmly adsorbed by the acid aluminum oxide, and it cannot be washed through the column by large quantities of distilled water. On the other hand, inorganic mercury and noncarboxylic organic mercury compounds can be recovered quantitatively from the column by small volumes of water. Acid aluminum oxide apparently has a large capacity for adsorbing meralluride, since 5 gm. of the adsorbent retains more than 8 mg. of meralluride mercury.

These observations were used in an attempt to isolate the mercurial excretory products following the administration of meralluride to dogs and, later, to normal subjects and patients in heart failure. It seems reasonable to conclude that diuresis is produced by the mercurial compound or compounds represented by the adsorbed fraction, since the excretory rate of this fraction closely parallels the diuresis and the increase of sodium excretion in the urine. The amount of mercury in the fraction passing through the column is insignificant and inadequate in amount to produce diuresis, and it probably represents degradation products of meralluride. We have previously found that a minimum of 15 mg. of meralluride mercury must be excreted every 24 hours to produce significant diuresis.[5] In no patient does the unadsorbed fraction, the degradation product, approach this amount. In patients who are resistant to mercurial diuretics and therefore excrete the meralluride slowly, however, the degradation products of meralluride greatly increase, suggesting that the retention of meralluride within the body leads to a breakdown of meralluride into a noncarboxylic form.

Summary and Conclusions

A column of acid aluminum hydroxide strongly adsorbs organomercurial compounds containing a carboxylic group, whereas noncarboxylic organic mercury compounds and inorganic mercury are readily washed through the column by distilled water. The carboxylic acid mercurial compound is completely eluted from the column by sodium carbonate solution. The adsorbent makes it possible to separate meralluride, an organomercurial containing a carboxyl group, from inorganic mercury, or from organomercurial agents that do not have a carboxyl group.

When urine obtained from a dog during meralluride diuresis is passed through an acid aluminum oxide column, 2 fractions of mercury are obtained. One, which represents by far the largest amount, is strongly adsorbed by the column. The other fraction is washed through the column by distilled water. Diuresis is closely related to the compound adsorbed by the column. Actually, the concentration of the nonadsorbed fraction is usually negligible, even during periods of considerable diuresis.

Similar observations have been made on normal human subjects and patients with heart failure. In normal human subjects, the excretory rate of mercury is not as rapid as in the dog, the total average 24-hour excretion rate being about 80 per cent. There is little difference between the normal subject and the patient with heart failure, except in the patient with moderate to severe failure who has marked edema; in such a patient, the rate of excretion is retarded, particularly following intramuscular administration. Patients who are unresponsive to mercurial diuretics exhibit a tendency to retain the mercury. This is accompanied by a significant increase in the degradation products.

References

1. HANDLEY, C. A. & R. A. SEIBERT. 1956. Chromatographic fractionation of the urinary excretory products of meralluride. J. Pharmacol. Exptl. Therap. **117:** 253.
2. LAUG, E. P. & K. W. NELSON. 1942. J. Assoc. Offic. Agr. Chemists. **25:** 399.
3. HANDLEY, C. A., D. CHAPMAN & J. H. MOYER. 1951. Some pharmacological properties of three new mercurial diuretics. Proc. Soc. Exptl. Biol. Med. **78:** 433.
4. NUHFER, P. A. & S. WHITE. 1951. J. Pharmacol. Exptl. Therap. **101:** 30.
5. MOYER, J. H., C. A. HANDLEY & R. A. SEIBERT. 1952. Clinical diuretic studies on three new mercurial compounds. Am. Heart J. **44:** 281.

RENAL TOLERANCE TO LONG-TERM ADMINISTRATION OF ORGANOMERCURIAL DIURETICS

By William A. Leff and Harvey E. Nussbaum
Hospital of St. Barnabas and for Women and Children, Newark, N. J.

The use of organomercurials as therapeutic agents frequently engenders an unwarranted fear of their possible toxicity. Heretofore the following challenging questions have remained either unanswered or unsatisfactorily answered:

(1) What are the possibilities that *inorganic* mercury will be deposited in the tissues during the course of therapy with *organo*mercurials?

(2) How much mercury can be demonstrated quantitively in the kidneys and other vital organs after extensive use of mercurial diuretics?

(3) Does impairment of renal function or permanent renal damage result from their use?

(4) Would adequate renal-function tests reveal damage to the kidney?

These questions presented a poignant challenge to us after the first 12 months of a long-term investigation[1] of the effectiveness of the oral organomercurial diuretic chlormerodrin (Neohydrin).* Our patients were taking very large amounts of Neohydrin by mouth following many years of therapy with parenteral meralluride sodium solution (Mercuhydrin). The answers to our questions regarding possible toxicity were to be found only by further clinical observation and laboratory tests.

We can now present the results of 4 years' investigation, including clinical data, results of renal function tests, autopsy findings, and the analysis of the vital organs for mercury. The information obtained is unequivocal evidence showing that massive cumulative doses of the oral organomercurial Neohydrin, following several years of therapy with Mercuhydrin, were completely harmless. These results make possible a greater optimism concerning the future use of oral organomercurial diuretics.

Early Clinical Results

During the past 4 years, 48 patients in chronic congestive heart failure have been maintained in fluid balance with the use of Neohydrin, maintenance digitalis, and low-salt diet. Five additional patients developed gastrointestinal symptoms, including nausea, loss of appetite, vomiting, and diarrhea, and they could not tolerate the drug, regardless of rest periods or reduced dosage. These 5 cases were considered failures, and are not included in this long-term report.

The initial functional classification of the patients varied from class II to class IV, under the criteria of the American Heart Association, Inc., New York, N. Y. Those in class IV were reduced to class II or III by active treatment with parenteral Mercuhydrin before changing to the oral regimen with Neohydrin. Most of the patients had received the parenteral diuretic for several years before the change to Neohydrin was made.

---

*Neohydrin supplied through the courtesy of H. L. Daiell, Lakeside Laboratories, Inc., Milwaukee, Wisc. Neohydrin is the registered trade-mark name for chlormerodrin (3-chloromercuri-2-methoxy-propylurea), a nonionic crystalline organomercurial.

TABLE 1
ETIOLOGY

Arteriosclerotic heart disease (A.S.H.D.)	22
Hypertensive cardiovascular disease (H.C.V.D.)	9
Hypertensive arteriosclerotic heart disease (H.A.S.H.D.)	2
Rheumatic heart disease (R.H.D.)	11
Luetic heart disease (L.H.D.)	4
	48

TABLE 2
AGE AND SEX

Age	Male	Female	Total
20–29	0	1	1
30–39	1	2	3
40–49	5	4	9
50–59	12	6	18
60–69	7	6	13
70–79	1	2	3
80	0	1	1
	26	22	48

The etiology of heart disease was varied (TABLE 1) and the age group ranged from 28 to 80 years (TABLE 2). Sixty-seven per cent were in the fifth and sixth decades. Dosage of Neohydrin varied with the response and tolerance of the patient (TABLE 3).

During the initial period of observation, 43 patients were maintained free from any signs or symptoms of congestive failure and did not require additional parenteral mercurials. Five patients *did* require occasional booster injections of Mercuhydrin in addition to the daily Neohydrin. After several weekly injections of Mercuhydrin, it became possible once more to maintain these patients on the daily oral mercurial for as long as 3 to 7 months before they required additional Mercuhydrin. Three patients developed diarrhea when taking 4 tablets daily. These patients were kept off the drug for 2 weeks, and then were given 1 tablet a day for 1 week. After this, the dose was increased each week until 3 tablets a day, following meals, were being taken. Two of

TABLE 3
DOSAGE

Neohydrin (tablets per day)	Mercury equivalent	Number of patients
2	20 mg.	11
3	30 mg.	29*
4	40 mg.	8†
		48

* Includes 2 patients maintained on 1 tablet per day after the first 6 and 9 months, respectively.
† Includes 1 patient who occasionally took 6 tablets per day.

TABLE 4
MERCURY ADMINISTERED

Mercury	Patient	Age	Sex	Etiol.	Urine	B.U.N.	Creat.	N.P.N.	C_{urea}
mg.									%
78,560	E.S.	64	F	A.S.H.D.	N	10.8	1.4	33	129 44
64,320	A.P.	73	F	A.S.H.D.	N	19.6 10.5	0.9	29.4	109 125
63,520	C.B.	59	M	H.C.V.D.	N	12.3 25 14.4	1.3	25	95 85
63,280	J.H.	58	M	H.C.V.D.	N	22	2		
60,320	M.S.	58	M	A.S.H.D.	N	10.7		22	90 94
14,960	M.E.	40	F	R.H.D.	Occ. Alb.	10	1.6	22	
14,920	C.M.	59	M	A.S.H.D.	N	14	1.4	24	
12,400	D.B.	62	M	R.H.D.	N	8.4	1	17.4	101
10,640	L.P.	53	F	A.S.H.D.	N	12.4			
6,240	S.H.	67	M	H.A.S.H.D.	N	14.4	1.8		

this group have had no further diarrhea; the third patient had soft stools about every fourth month during the 3-year period. This was corrected by abstinence from the drug for 2 weeks, after which it was resumed, as described. None of the patients developed any symptoms of mercurialism or any similar reactions ascribable to mercurial hypersensitivity.

The results of the first-year study convinced us that most patients in chronic congestive failure could be maintained in fluid balance with the oral mercurial Neohydrin and maintenance digitalis. We were not sure, however, as to the long-term effects of the large doses of mercury upon the kidneys and other organs. Therefore, in the subsequent 3 years of this investigation, great stress was laid on performing kidney-function tests on the patients. Clinically, attention was concentrated on the search for any evidence of renal insufficiency or renal damage. The over-all plan also included histologic study of tissues obtained at autopsy for evidence of mercurial damage, and quantitative tissue analysis for "metallic mercury" in the whole organs.

In the 4 years of our study, the combined total of mercury contained in both parenteral and oral organomercurials given to 48 patients ranged from 6240 mg. to 78,560 mg. TABLE 4 shows the amounts of mercury taken as organomercurial by the 5 patients receiving the highest and lowest totals. The majority of the patients—34, or 71 per cent—received a combined dosage ranging from 20,000 to 60,000 mg. of bound mercury.

Later Clinical Results

The following 3 years of our 4-year experience with Neohydrin have proved conclusively its effectiveness as a thoroughly safe and potent "continuous diuretic" agent. Once the dry-weight level was achieved with parenteral Mercuhydrin, the "see-saw" of accumulation and dehydration was seen rarely. The steady diuretic effect of Neohydrin was in sharp contrast to the intermittent diuretic effect of periodic injections. In several patients, however, an occasional booster shot of the parenteral agent seemed to enhance the steady action of the oral organomercurial. The 48 patients included in this report showed no evidence of mercurial toxicity, as manifested by skin reactions, allergic phenomena (hypersensitization to mercury), renal damage, cardiovascular reactions, bone-marrow depression, or systemic reactions.

The effectiveness of Neohydrin in the older age group continued to be striking. It is obvious that men and women in myocardial failure are now living much longer, due to more accurate diagnosis, the newer glycosides, sodium-restricted diets, and the use of effective nontoxic organomercurials. It should be emphasized that the aged can tolerate oral organomercurials without difficulty and without renal toxicity.

In the entire series, there was no clinical or laboratory evidence of renal impairment or permanent renal damage due to the massive cumulative dosage of parenteral and oral organomercurial. In spite of the tremendous total dosages, it will be noted (TABLE 5) that there were practically no abnormal urinary findings. Seven patients exhibited occasional low-grade (1+ to 2+) albuminuria, but it is not unreasonable to suppose that this was due to renal passive congestion and not to any effect of the diuretic. Race and his coworkers,[2] at the Mayo Clinic, Rochester, Minn., recently reported that albuminuria existed in 88 per cent of a group of 161 patients with congestive failure who had come to autopsy without clinically obvious causes for albuminuria, and who showed no histologic changes that would account for albuminuria. There was a tendency for the albuminuria to parallel the severity of the cardiac failure.

Of greater significance in our own laboratory data were the consistent findings of normal blood-urea nitrogen throughout this study. In fact, urea nitrogen improved in some patients while they were taking the medication, which is a manifestation of improved cardiovascular-renal dynamics. In addition, there were the noteworthy normal findings of blood creatinine, nonprotein nitrogen (N.P.N.), and urea clearance tests.

Deaths During Study

There were 8 deaths in the series of patients, none of which were related to mercury (TABLE 6). Three patients died suddenly of coronary thrombosis. They had been completely free of any signs and symptoms of failure up to the day of death. A fourth patient died of toxemia and acidosis following the amputation of a leg, necessitated by saddle embolism. She was not in failure at the time of the embolic accident. Another patient had syphilitic heart disease with aneurysmal dilatation of the aorta, and aortic insufficiency with marked hypertrophy of the left ventricle. He died suddenly, following an episode of severe chest pain. Permission for autopsy was not obtained, but the clinical picture suggested a ruptured aneurysm with hemorrhage. He showed no signs of failure up to the time of death.

Permission for autopsy was obtained for the 3 other patients who died during the study.

TABLE 5

Patient	Age	Sex	Race	Etiology	NEOHYDRIN*				MERCUHYDRIN†			TOTAL MERCURY	Complications	LABORATORY STUDIES				
					Daily dose (tablets)	Duration (yrs.)	Duration (mos.)	Total mercury (mg.)	Weekly dose (c.c.)	Duration (yrs.)	Total mercury (mg.)	Oral and parenteral (mg.)		Urine	Urea nitrogen	Creatinine	N.P.N.	Urea clearance
																		%
1. C. B.	59	M	C	H.C.V.D.	2 b.i.d.	1	9	23,520	2	10	40,000	63,520	0	N	12.3 25 14.4	1.3	25	95
2. D. B.	62	M	C	R.H.D.	1 b.i.d.	1	3	8,400	2	1	4,000	12,400	0	N	8.4	1	17.4	101
3. E. B.	57	F	C	R.H.D.	1 b.i.d.	1	7	10,640	4	3	24,000	34,640	0	N	9	0.8	18	94
4. E. B.	53	M	C	H.C.V.D.	1 b.i.d.	1	8	11,200	2	3	12,000	23,200	0	N		0.4	22	
5. F. B.	67	F	C	H.C.V.D.	1 t.i.d.	1	7	15,960		None		15,960	0	N	10.4		21	100
6. H. B.	30	M	C	R.H.D.	1 t.i.d.	3	0	30,240	2	3⅓	13,330	43,570	0	N	12		15	
7. S. B.	80	F	C	A.S.H.D.	1 t.i.d.	2	0	20,160		None		20,160	0	N				
8. M. C.	59	F	W	H.A.S.H.D.	1 b.i.d.	2	0	13,440	2	1	4,000	17,440	0	N				
9. T. C.	45	M	C	L.H.D.	1 t.i.d.	3	0	30,240	2	2	8,000	38,240	0	Albumin; few	14.3 12.9	1.4	32.4	155
10. W. C.	62	M	C	H.A.S.H.D.	1 t.i.d.	1	10	18,480	4	1	8,000	26,480	0	N	13.5	1.3	28.2	193 177
11. E. D.‡§	28	F	W	R.H.D.	1 t.i.d. 1 o.d.	 2	6 3	12,600	2	2½	10,000	22,600	0	N	11.5	1	20	
12. F. D.	59	M	W	A.S.H.D.	1 t.i.d.	2	6	25,020	1	1	2,000	27,020	0	N	12	1.2	12	
13. R. D.	45	M	W	R.H.D.	1 q.i.d.	2	0	26,880	4	3	24,000	50,880	Post-commissurotomy	N	11.3			88.4
14. M. E.	40	F	W	R.H.D.	1 b.i.d.	1	4	8,960	1	3	6,000	14,960	0	Occ. albumin	10	1.6	22	
15. B. F.	54	M	W	A.S.H.D.	1 t.i.d.	2	0	20,160	2	1	4,000	24,160	0	N	15			
16. D. G.‡§	50	M	C	R.H.D.	1 t.i.d.	2	0	20,160	2	½	2,000	22,160	0	N	10.6 19.2	1.4	30	
17. E. G.	46	F	C	H.C.V.D.	1 b.i.d.	1	6	10,080	2	5	20,000	30,080	Grade 3 retinopathy	Alb. trace	15	1.2		
18. G. G.	48	M	W	A.S.H.D.	1 t.i.d.	2	0	20,160	2	2	8,000	28,160	0	N	12.4	1.1		
19. J. G.	62	M	C	L.H.D.	1 t.i.d.	2	0	20,160		None		20,160	Anemia; luetic nephrosis; heart block	Alb. 4+ prior to oral diuretic therapy				
20. N. G.‡	67	F	W	A.S.H.D.	1 b.i.d.	2	6	16,800	2	2	8,000	24,800	0	N	16.5	2		
21. F. H.‡	48	M	C	L.H.D.	1 t.i.d.	3	0	30,240	2	4	16,000	46,240	0	N	15	1.8	28.1	92
22. J. H.	58	M	C	H.C.V.D.	1 t.i.d.	3	6	35,280	2	7	28,000	63,280	0	N	22	2		
23. S. H.‡	67	M	W	H.A.S.H.D.	1 b.i.d.	0	4	2,240	2	1	4,000	6,240	0	N	14.4	1.8		
24. M. J.	72	M	C	A.S.H.D.	1 t.i.d.	1	0	10,080	2	2	8,000	18,080	0	N				
25. J. K.	68	F	C	A.S.H.D.	1 t.i.d.	2	0	20,160	2	2	8,000	28,160	Kimmelstiel-Wilson disease, diabetes	Alb. 4+	10.9	1.8		
26. J. K.	47	M	W	A.S.H.D.	1 t.i.d.	3	6	35,280	1	2	4,000	39,280	0	N	11	1.2	24	

27. E. L.‡§	48	F	W	R.H.D.	1 q.i.d.	1	6	20,160		None		20,160	0	Alb. 1+	24 21.9	2.1	42 40	
28. C. M.	59	M	W	A.S.H.D.	1 t.i.d. 1 o.d.	0	9	10,920	1	2	4,000	14,920	0	N	14	1.4	24	
29. H. M.	52	M	W	A.S.H.D.	2 b.i.d.	1	3	16,800	2	2	8,000	24,800	0	N				
30. M. M.‡	71	F	C	A.S.H.D.	1 t.i.d.	0	7	5,880	2	4	16,000	21,880	0	Occ. albumin	18	2		
31. R. M.	57	M	C	A.S.H.D.	2 b.i.d.	2	0	26,880	1	1	8,000	34,880	0	N	10.1 12.5		24	
32. R. M.	57	M	W	A.S.H.D.	1 b.i.d.	2	10	19,040	2	2	8,000	27,040	0	N	15			
33. E. N.	67	F	C	L.H.D.	2 b.i.d.	1	5	19,040	2	1	4,000	23,040	0	N				
34. A. P.	73	F	C	A.S.H.D.	1 t.i.d.	4	0	40,320	2	6	24,000	64,320	0	N	19.6 10.5	0.9	29.4	109 125
35. A. P.	60	F	W	R.H.D.	1 t.i.d.	2	6	25,200		None		25,200	0	N				
36. B. P.	49	F	C	H.C.V.D.	2 b.i.d.	1	6	20,160		None		20,160	0	N	13.8			
37. F. P.‡	65	M	C	A.S.H.D.	1 t.i.d.	1	0	10,080	2	2½	10,000	20,080	0	N	15.4	1.4		
38. F. P.	56	M	W	A.S.H.D.	1 t.i.d.	2	0	20,160	2	3	12,000	32,160	Occ. loose stool	N	14	1.2	30	84 92
39. J. P.	60	M	C	A.S.H.D.	1 t.i.d.	2	6	25,200	2	1	4,000	29,200	0	N				
40. L. P.	53	F	C	A.S.H.D.	1 b.i.d.	1	7	10,640		None		10,640	0	N	12.4			
41. R. P.	63	M	C	A.S.H.D.	1 t.i.d.	3	6	35,280	2	1	4,000	39,280	0	N	9.8			
42. E. S.	64	F	C	A.S.H.D.	2 b.i.d.	3	2	42,560	2	9	36,000	78,560	0	N	10.8	1.4	33	129 44
43. E. S.	58	F	C	H.C.V.D.	1 t.i.d.	3	0	30,240		None		30,240	0	Occ. casts	14.7 22.8	1.2 1.8	34.2	66.6 51.3
44. L. S.	55	F	C	H.C.V.D.	1 t.i.d.	1	10	18,480		None		18,480	0	N	24 18			
45. M. S.	58	M	W	A.S.H.D.	1 t.i.d.	4	0	40,320	2	5	20,000	60,320	0	N	10.7		22	90 94
46. R. S.	38	F	C	R.H.D.	1 b.i.d.	3	0	20,160	2	4	16,000	36,160	0	N	15		38.7	86.2 90
47. E. T.	55	F	C	A.S.H.D.	1 t.i.d.	3	6	35,280	2	2½	10,000	45,280	0	N				100 disability
48. C. W.	30	F	C	R.H.D.	1 t.i.d.	3	2	31,920	2	1	4,000	35,920	0	N	11 15	0.9 1.2	27 38	148 119

---

* Chlormerodrin (Neohydrin) contains 10 mg. of mercury per 18.3 mg. tablet.
† Meralluride (Mercuhydrin) contains 39 mg. of mercury per cc. of solution.
‡ Died during study.
§ Autopsy performed.

TABLE 6
DEATHS DURING NEOHYDRIN STUDY

Duration	Patient	Age	Etiology	Cause of Death
mo.				
7	M.M.	71	A.S.H.D.	Acute coronary thrombosis
4	S.H.	67	H.A.S.H.D.	Acute coronary thrombosis
12	F.P.	65	A.S.H.D.	Acute coronary thrombosis
30	N.G.	67	A.S.H.D.	Embolism to femoral artery; amputation
36	F.H.	48	L.H.D.	Aortic aneurysm
18	E.L.	48	R.H.D.	Pulmonary embolism
24	D.G.	50	R.H.D.	Congestive failure (subclinical)
33	E.D.	59	R.H.D.	(1) Endocarditis, acute bacterial, of mitral and tricuspid v. (2) Subacute and chronic pyelonephritis (3) Nephrosclerosis, benign

When patient E. L. was seen in the clinic, she was classified as having mitral stenosis and insufficiency, and questionable aortic insufficiency with slight hypertrophy of the right and left ventricle, class II. She was maintained in fluid balance with digitalis and a low-salt diet for 2 years. She then presented evidence of acute rheumatic fever and her failure increased to class IV. She was hospitalized and improved considerably on symptomatic therapy. She was then followed in the clinic as a class II patient, on Neohydrin (4 tablets daily; 40 mg. Hg), in addition to maintenance digitalis and a salt-free diet. She remained in fluid balance for 18 months on this regimen. She was later seen by a private physician who advised her that she did not require digitalis or Neohydrin. Twelve weeks later she was admitted to the hospital in a moribund condition with irreversible failure. She did not respond to any therapy and died suddenly.

The post-mortem examination showed a rheumatic calcified mitral valve and a partially calcified aortic valve with hypertrophy of both right and left ventricles. There was a large hemorrhagic infarct of the right lower lobe.

Sections of the kidney (FIGURE 1) showed cloudy swelling in the tubules with some increased cellularity of the glomerulus. There was no evidence of tubular necrosis.

Sections of the liver (FIGURE 2) showed congestion around the central vein with hemosiderin deposits. There was no disruption of liver architecture.

This patient, E. L., received Neohydrin equivalent to 20,160 mg. of mercury. Analysis of the internal organs for retention of mercury demonstrated that the kidney contained only 11.48 mg. of mercury per 100 gm. of dry tissue. Comparable amounts for the other organs are shown in TABLE 7.

The second autopsy was on D. G., a 50-year-old Negro with rheumatic aortic stenosis, mitral stenosis, and insufficiency, who was classified class II and was kept in fluid balance with Neohydrin (equivalent to 30 mg. Hg daily) for 2 years, along with maintenance digitalis and a salt-free diet. He received 2 c.c. of Mercuhydrin weekly for 6 months prior to attending the cardiac clinic.

This patient developed a bradycardia of 40 with atrioventricular block, and and had several episodes of the Adams-Stokes syndrome. During these at-

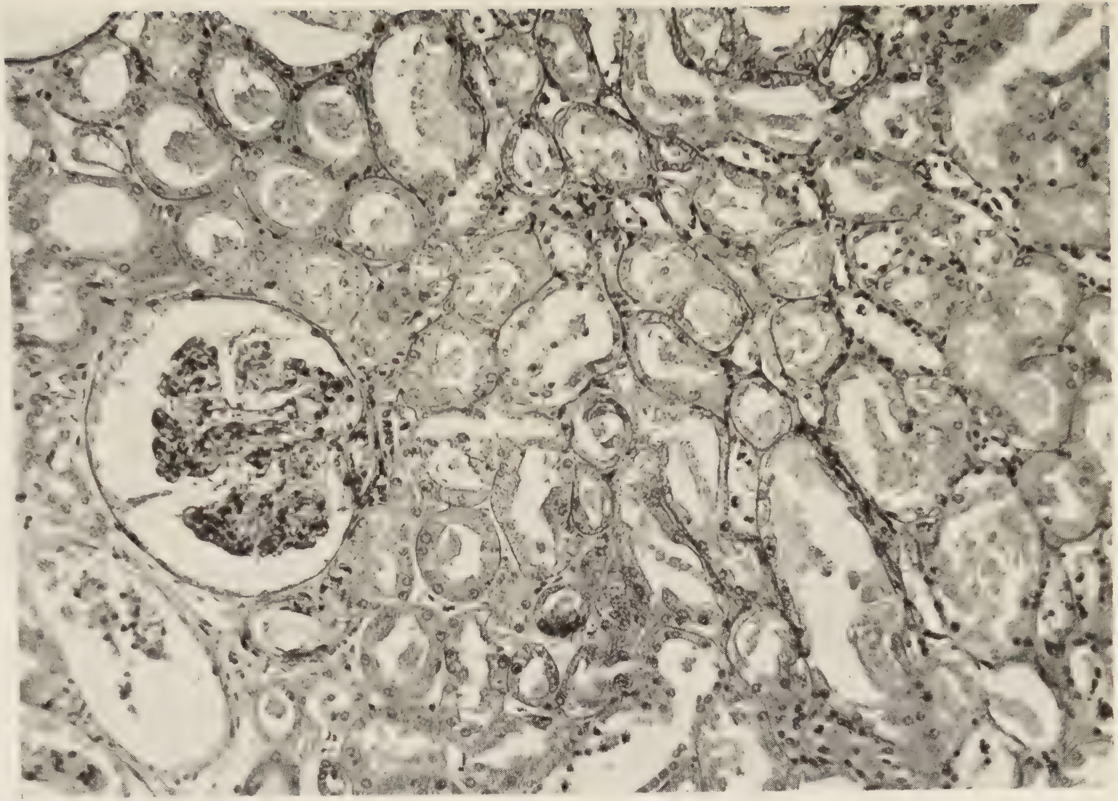


FIGURE 1. Kidney from patient E. L., female, age 48 years, with rheumatic heart disease. This patient received Neohydrin and Mercuhydrin equivalent to more than 20,000 mg. of mercury. Renal tissue shows congestion, with moderate glomerulonephritis. ×100.

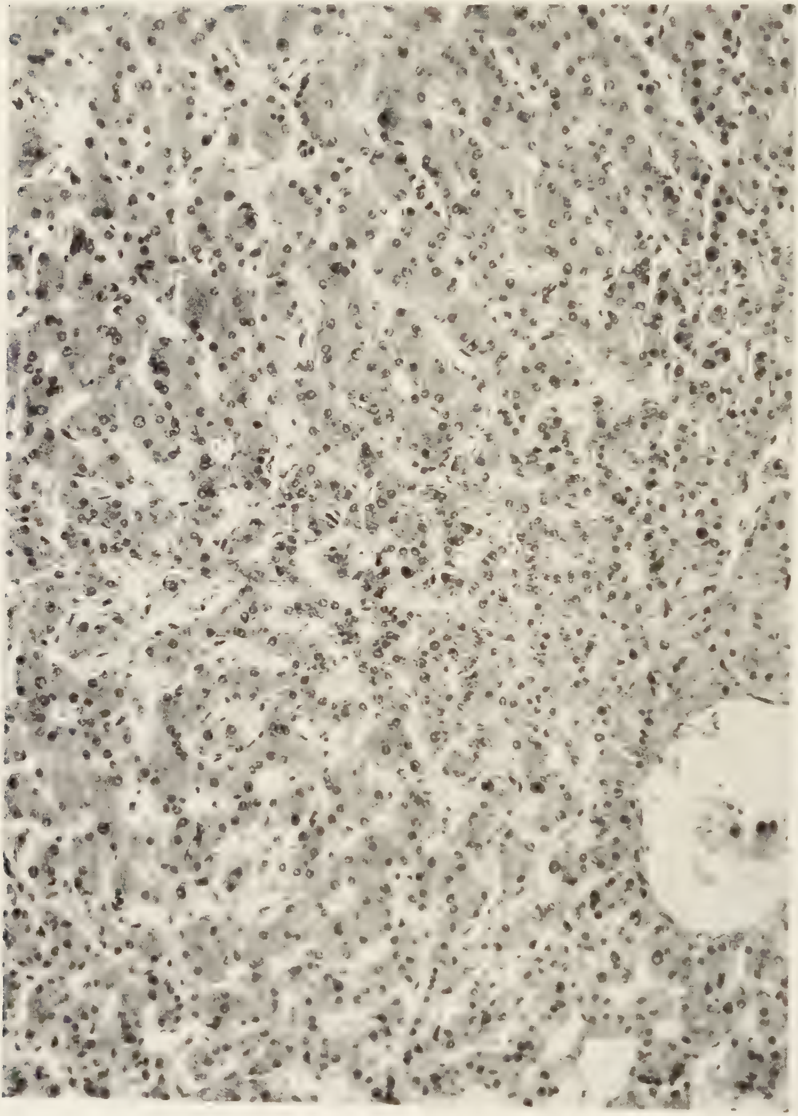


FIGURE 2. Liver from patient E. L. Tissue shows only passive congestion and early mild portal cirrhosis. ×100.

TABLE 7

TISSUE ANALYSIS FOR MERCURY

Mg. per 100 gm. Dried Tissue

Patients	Organomercurial (mg.)	Kidney	Liver	Spleen	Heart	Large intestine	N.P.N.
			Griffith *et al.**				
15	None	2.05	0.37	0.12	—	—	122†
14	400 mg. or less	2.96	0.34	0.04	—	—	66
16	400 mg. or more (avg.: 4692)	15.29	1.38	0.32	—	—	73
			Leff and Nussbaum				
E.L.	20,160	11.48	0.694	—	0.0144	1.34	20
D.G.	22,160	9.63	0.474	—	0.0006	0.4	30
E.D.	22,600	15.68	0.773	0.221	None	7.3	40 42

* Values shown from Griffith, Butt, and Walker[3] are averages for patient groups.

† Based on 4 patients, 1 having marked uremia.

tacks he did not show any clinical signs of failure. The last episode of syncope for which he was hospitalized showed electrocardiographic evidence of complete dissociation, with a ventricular rate of 34. In the ensuing 10 days he slowly developed irreversible myocardial failure in spite of all therapy and died on the 12th day of hospitalization.

Post-mortem examination showed aortic and mitral stenosis with hypertrophy of the right and left ventricles.

Sections of the kidney showed no tubular necrosis (FIGURE 3). The basement membrane of the tubules appeared sharp, without any disruption of its normal architecture.

Sections of the liver showed congestion about the central vein, with deposits of hemosiderin (FIGURE 4). There was no damage to the liver cells.

Another patient, D. G., received Neohydrin and Mercuhydrin equivalent to 22,160 mg. of mercury. Analysis of tissues for mercury, however, showed a concentration of only 9.63 mg. per 100 gm. of dry tissue, and correspondingly small amounts in other organs. Note that the amount detected in cardiac tissue was negligible (TABLE 7). The third autopsy was on patient E. D., a 28-year-old woman with rheumatic heart disease. She was a class II cardiac with mitral stenosis and insufficiency and aortic insufficiency. She had received weekly parenteral organomercurial therapy (Mercuhydrin, 2 c.c.) for $2\frac{1}{2}$ years prior to attending the clinic. She was then placed on Neohydrin, 3 tablets equivalent to 30 mg. Hg a day, for 6 months. At the end of that period she required only 10 mg./day, which she continued for 2 years and 3 months. She also received prophylactic oral penicillin. She then developed symptoms and signs of bacterial endocarditis that were proved by blood cultures, but she did not respond to therapy in spite of massive combined antibiotic therapy. The terminal clinical picture was one of myocardial failure.

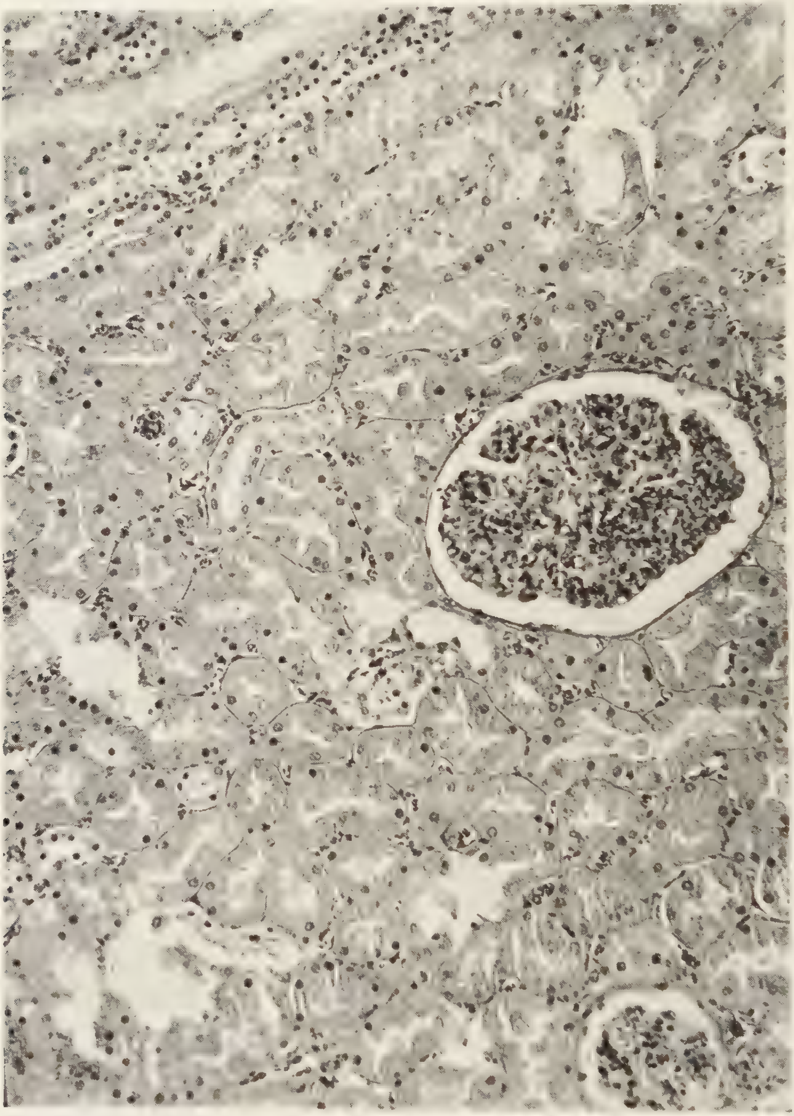


FIGURE 3. Kidney from patient D. G., male, age 50 years, with luetic heart disease. This patient received organomercurial diuretics equivalent to more than 22,000 mg. of mercury. Renal tissue shows congestion, without tubular necrosis. ×200.

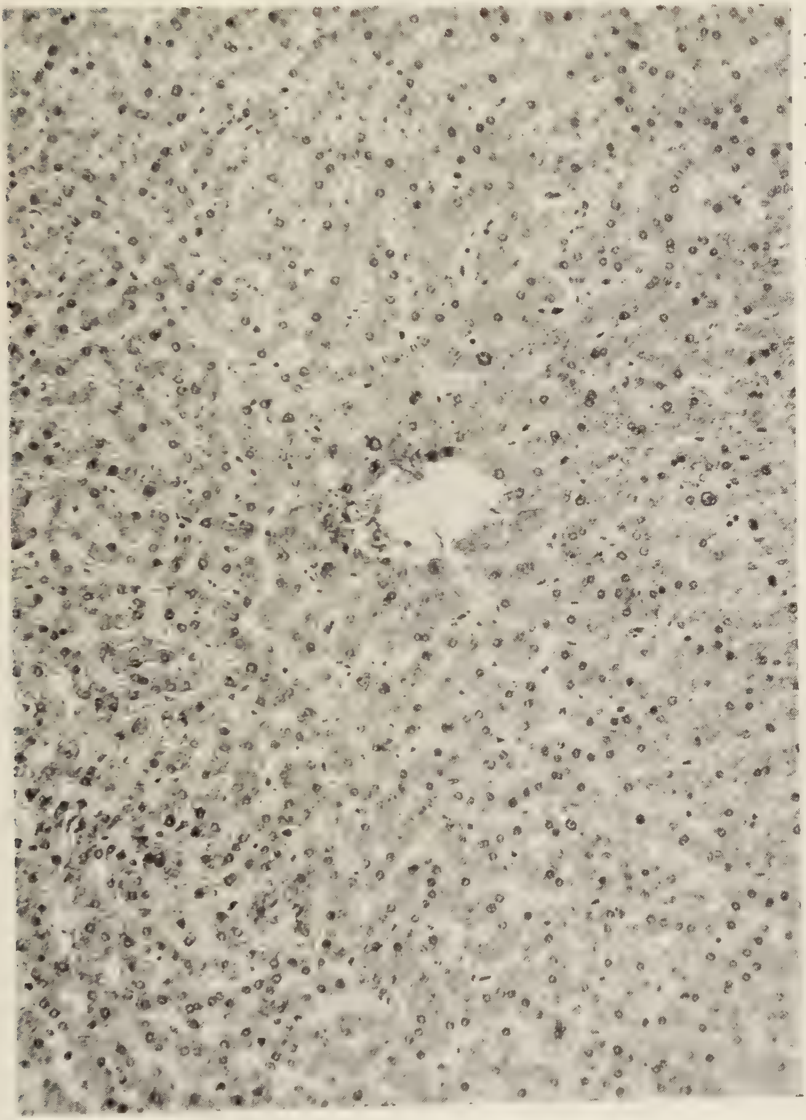


FIGURE 4. Liver from patient D. G. No damage to cells. Congestion surrounding central vein, with deposits of hemosiderin. ×200.

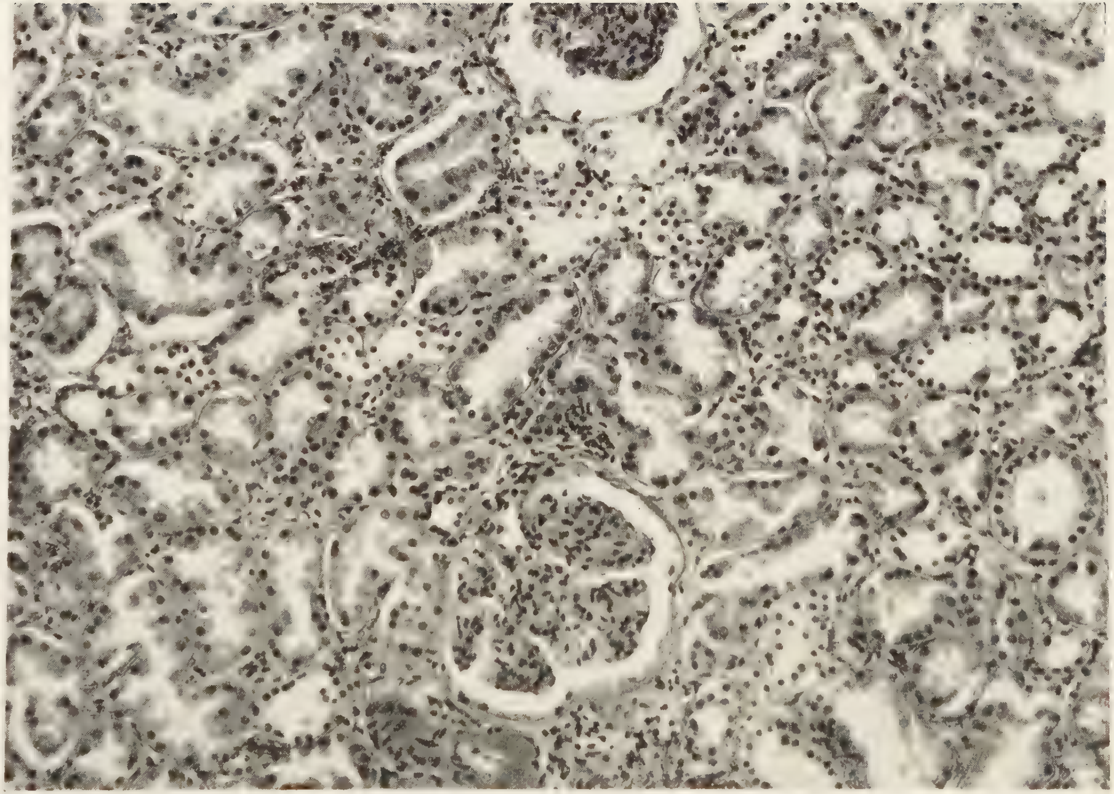


FIGURE 5. Kidney from patient E. D., female, age 59 years, with rheumatic heart disease. This patient received organomercurials equivalent to more than 22,000 mg. of mercury. Thickening of glomerular capsule and of tubular basement membrane, without tubular inflammation or necrosis. ×200.

The post-mortem examination revealed acute and chronic endocarditis of the mitral and tricuspid valves, hypertrophy of the right and left ventricles, subacute and chronic pyelonephritis, benign nephrosclerosis, and chronic passive congestion of the liver.

Sections of the kidney showed some thickening of the capsule of the glomerulus and thickening of the basement membranes of the tubules (FIGURE 5). There was no inflammation or necrosis of the tubules. Some sections showed thickening of the smaller arterioles.

Sections of the liver showed congestion, edema, and deposits of hemosiderin (FIGURE 6). There was no evidence of necrosis. This patient, E. D., received the equivalent of 22,600 mg. of mercury as organomercurial diuretics. Her kidneys contained less than 16 mg. of mercury per 100 gm. of dry tissue. It is notable that in this case, which, of our 3 patients, contains the greatest concentrations in the kidneys, liver, and large intestine (TABLE 7), no mercury was detected in the cardiac tissue. In all 3 cases the mercury content of the heart muscle was infinitesimal. This analysis offers strong evidence against the direct action of mercury from organomercurial diuretics upon the heart muscle.

Thus none of our patients who came to autopsy showed evidence of any glomerular, renal tubular, hepatic, or cardiac pathology attributable to mercury.

Tissue Mercury Findings

It is interesting to compare our analyses of human tissues for mercury with a study by Griffith, Butt, and Walker.[3] These investigators analyzed the organs of 45 patients with congestive heart failure. Of the group studied, 15 patients had no record of having received mercury. The amounts of mercury found in their tissues are shown in the top line of TABLE 7. Since both young and old individuals were included in this group, it may be assumed that traces of mercury may be found in the tissues at all ages.

Therapeutically, 14 persons received 400 mg. or less of organomercurial, and 16 persons received 400 mg. or more. The latter group averaged 4692 mg. The mercury contents of their livers, spleens, and kidneys are shown in TABLE 7. Only 4 of the 15 patients who had received no mercury were available for nonprotein nitrogen (N.P.N.) studies. One of them had marked uremia, which made the average N.P.N. for the group spuriously high 122 mg. per 100 c.c.[3] The N.P.N. values for the patients who *had* received mercury as organomercurial were considerably smaller. Griffith concluded that the N.P.N. values could not be interpreted as indicating that the amounts of mercury in the tissues of these patients were harmful.

It should be noted that two thirds of Griffith's cases involved renal disease, but not of the type caused by mercurial damage or toxicity. The high N.P.N.s were consistent with the type of renal pathology.

In our own patients, the amounts of organomercurial received were all in a narrow range just above 20,000 mg. of mercury. This range is roughly 5 times as great as Griffith's highest average, and about 50 times greater than the average for his patients who received less than 400 mg. of mercury. N.P.N.

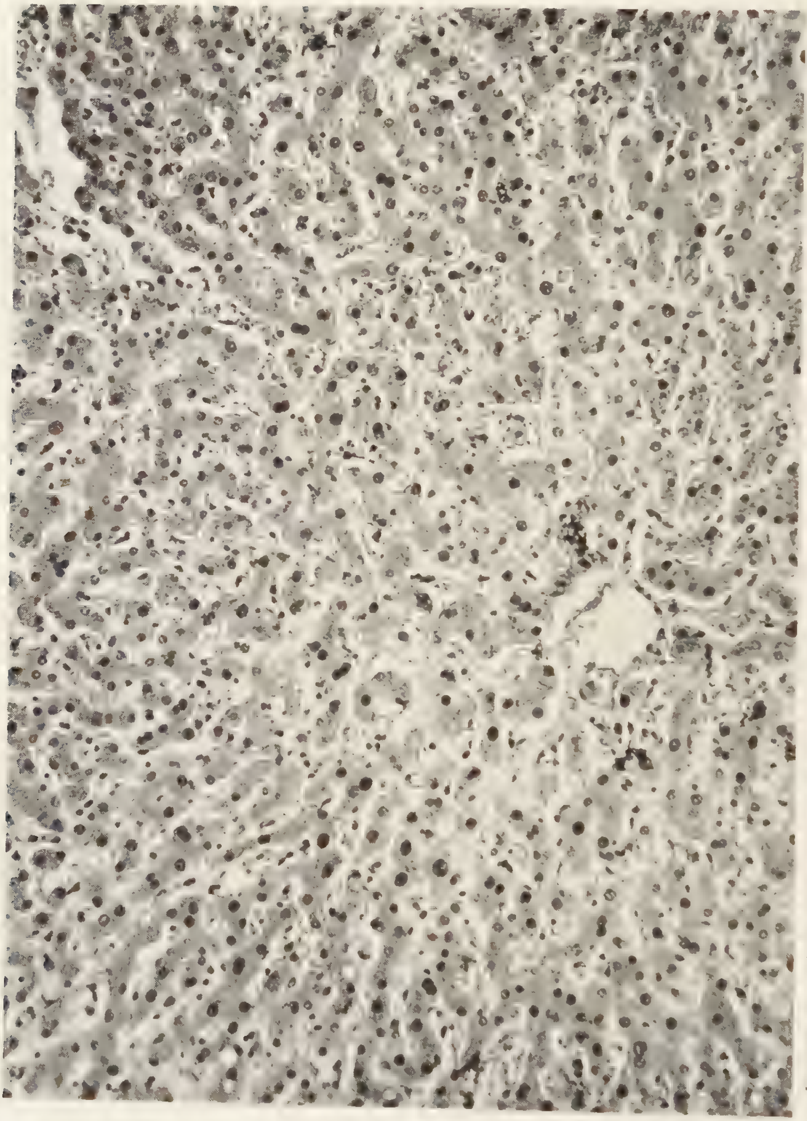


FIGURE 6. Liver from patient E. D. No evidence of necrosis. Section shows congestion and edema, with deposits of hemosiderin. ×200.

TABLE 8

KIDNEY DISEASE IN 45 CASES REPORTED BY GRIFFITH, BUTT, AND WALKER[3]

Disease	15 Cases; No Hg	14 Cases; 400 mg. Hg or less	16 Cases; 400 mg. Hg or more
Nephrosis	2	2	2
Renal infarct	1	0	2
Pyelonephritis	0	1	2
Nephrosclerosis	6	6	5
Hydronephrosis	0	0	1
No disease	6	5	4

values were lower in our patients than the average N.P.N. values in Griffith's patients.

Despite the much larger amounts of organomercurial taken by our patients, the mercury content of the kidneys was less in 2 cases and about the same in 1 case. For some reason, in spite of the much greater total dosage, the mercury content of the kidneys of our patients was *not* proportionately higher than that of Griffith's patients.

Part of the difference between our results and those obtained by Griffith may be related to the large number of cases with renal pathology, unrelated to organomercurials, in the Griffith, Butt, and Walker[3] study (TABLE 8). Our case with highest kidney mercury content (E. D.) had pyelonephritis and benign nephrosclerosis. Our other 2 cases (E. L. and D. G.), both with low kidney mercury content, had no renal pathology. Apparently, relatively little mercury is accumulated in the "normal" kidney of the patient with congestive heart failure. On the other hand, even where there is advanced kidney damage from other causes, as in Griffith's patients and our patient E. D., only a slight increase in the content of mercury can be noted. The latter findings support the clinical thesis that organomercurials can be used in the presence of kidney damage as long as diuresis is constant.

Conclusions

As far as we are concerned, this clinical and laboratory investigation disproves the fear of an "inorganic mercury" effect from the retention of massive cumulative doses of parenteral and oral organomercurials. If there were a splitting-off of inorganic mercury ions from the large amounts of organomercurials used in this series, the effect upon the kidney should have been evident clinically, histologically, and in the tissue analysis. There was no mercury renal damage in any of these areas. Our clinical experience with these organomercurials, Mercuhydrin and Neohydrin, supports the concept of a "specific organic molecule," rather than a mercury action per se, as being responsible for the diuretic action. This concept was stressed by Saxl and Heilig[1] in their original description of the modern use of organomercurials as diuretics. The most recent edition of the pharmacology text by Goodman and Gilman[5] states that: "Older evidence suggested that the mercurials were active by virtue of their release of mercuric ion (Hg^{++}). However, it is more likely that organic mercury complexes dissociate as such and act in the form of the specific organic molecule, R —Hg$^+$." The N.N.R. specifications for Neohydrin[6] state explicitly that there be "absence of ionizable mercury and other heavy metals, as indicated by the standard sodium sulfide reaction." Such authorities as Kolmer,[7] Homer Smith,[8] and Moyer[9] conclude that mercurials are excreted as an organic compound, and that mercury is not split off in its metallic form.

Most prejudice against organomercurial diuretics is probably ascribable to the unsupportable assumption that modern organomercurials have the same basic toxicity as such toxic inorganic mercurials as bichloride of mercury and calomel. The few early organomercurials with significant toxicity, such as merbaphen (Novasurol) and esidron, have been out of use for many years, but their memory serves to prejudice the minds of many physicians.

Because the organomercurials are the most potent diuretics and are so vital in prolonging the life of the cardiac patient, the unwarranted fear of their prolonged use must be dispelled if we are to help the cardiac patient to more years of comfortable living and employment. The absence of mercurial toxicity in our patients who were observed for a 4-year period and who took massive total doses of organomercurials should remove all fear of the use of these important therapeutic agents. It is our opinion that the organomercurial drug is itself harmless, provided that the physician is master of his therapy at all times. He must be alert to signs or symptoms of allergy or sensitization to the medication. He must not permit the repeated use of the organomercurials (or of any other drug, for that matter) when such use elicits continued allergic reaction. Most of the so-called toxic reactions reported to be due to organomercurials might have been avoided if the physician had become aware of the symptoms of sensitivity.

Summary

(1) Forty-eight clinic patients in chronic congestive heart failure were maintained in a state of cardiac compensation with the oral organomercurial chlormerodrin (Neohydrin) over a 4-year period. All patients received maintenance digitalis and were advised to stay on a salt-free diet.

(2) An additional 5 patients treated during the 4-year period had gastrointestinal disturbances manifested by nausea, vomiting, and diarrhea. These patients were withdrawn from the study because of their inability to tolerate the drug.

(3) Thirty-nine of the 48 patients had previously received parenteral meralluride sodium solution (Mercuhydrin) from 6 months to 10 years prior to the initiation of therapy with the oral drug; the other 9 patients had never received parenteral organomercurials prior to therapy with Neohydrin.

(4) The combined total dosage of oral and parenteral mercury ranged from 6240 mg. to 78,560 mg. of mercury per patient, with no clinical evidence of renal toxicity due to the organomercurials.

(5) Renal function was tested in every patient by means of urinalysis and tests for urea nitrogen, N.P.N., and creatinine. Urea clearance tests were done in 17 patients. The sole abnormalities detected were occasional albuminuria in 7 patients.

(6) Of the 8 deaths in the series, none of which were related to toxicity of the diuretic, 3 came to autopsy. There was no gross or microscopic evidence of renal damage due to mercury.

(7) Tissue analysis revealed a small mercurial content in the kidneys, and infinitesimal amounts of mercury in heart muscle, liver, spleen, and large bowel.

(8) Neohydrin showed no evidence of renal toxicity over a 4-year period. Most so-called "toxic reactions" to organomercurial diuretic therapy can be eliminated by proper control of therapy in sensitive patients.

Acknowledgment

We thank the Essex County Heart Association, East Orange, N. J., for the services of Mrs. Ann Krug, who assisted in this study.

References

1. LEFF, W. & H. E. NUSSBAUM. 1953. Clinical investigation of the oral mercurial Neohydrin® over a one year period. J. Med. Soc. New Jersey. **50:** 149.
2. RACE, G. A., C. H. SCHEIFLEY & J. E. EDWARDS. 1956. Albuminuria in congestive heart failure. Circulation. **13:** 329.
3. GRIFFITH, G. C., E. M. BUTT & J. WALKER. 1954. The inorganic element of certain human tissues. Ann. Internal Med. **41:** 501.
4. SAXL, P. & R. HEILIG. 1920. Über die diuretische Wirkung von Novasurol und anderen Quecksilberpräparaten. Wien. klin. Wochschr. **33:** 943.
5. GOODMAN, L. & A. GILMAN. 1955. The Pharamacological Basis of Therapeutics. 2nd ed. Macmillan. New York, N. Y.
6. COUNCIL ON PHARMACY AND CHEMISTRY. New and Nonofficial Remedies. 1953. Chlormerodrin. J. Am. Med. Assoc. **152:** 331.
7. KOLMER, J. A. 1926. Chemotherapy, With Special Reference to the Treatment of Syphilis. Saunders. Philadelphia, Pa.
8. SMITH, H. W. 1951. The Kidney. Oxford Univ. Press. New York, N. Y.
9. MOYER, J. H., C. A. HANDLEY & R. A. SEIBERT. 1956. An analysis of the excretory products of a mercurial diuretic by column chromatography. Ann. N. Y. Acad. Sci. **65**(5): 511.

MASSIVE DOSES OF MERCURIAL DIURETICS IN REFRACTORY PATIENTS

By G. B. Gordon, I. Feder, and I. J. Greenblatt
Beth-El Hospital, Brooklyn, N. Y.

Despite the widespread and increasing use of mercurial diuretics, it is still not uncommon to find reports that question the margin of safety of the various compounds in current use. Similarly, much has been made of the nonmercurial composition of such other diuretic agents as acetazolamide (Diamox), thereby implying a low toxicity index for such drugs.

Because the question of toxicity still is raised occasionally where a choice of diuretics is at issue, especially in cases of long-term use, I am reporting on certain clinical and biochemical observations made during the past 7 years by I. Feder, I. J. Greenblatt, and myself, particularly on the use of massive doses of mercurial diuretics by intravenous administration.

The background for our work in administering massive doses by the intravenous route is the mounting evidence that there is no contraindication to the use of mercurials in therapeutic doses other than pre-existing severe renal insufficiency. Burch and his co-workers[1] have shown that about 50 per cent of injected mercury is removed by the kidneys and secreted with the urine within 3 hours by an average subject, and that virtually all of it is excreted within the first 24 hours. The oral diuretics are excreted with similar rapidity,[2] although our own research has indicated some difference in rates of excretion among the available compounds, so that, for example, chlormerodrin (Neohydrin) is excreted twice as rapidly as mercumatilin (Cumertilin).

While Pitts[3] has shown that the kidney is the major organ involved in such mercury concentration as occurs, Griffith, Butt, and Walker[4] and Leff *et al.*[5] have reported that studies of patients who have taken mercurial diuretics over periods of several years have shown no signs of damage, renal or otherwise.

In a group of patients under our observation for years, as much as 2000 mg. and, in some cases, in excess of 4000 mg. of mercury was introduced per year without any signs of toxicity as manifested by gum-line or bone-marrow depression, or renal complications. Sternal bone-marrow studies at 2- and 4-year intervals, and more frequent periodic peripheral blood counts clearly demonstrated that the long-term administration of meralluride sodium solution (Mercuhydrin) in these patients produced no blood pathology. TABLE 1 shows the bone-marrow reports, and particularly the normal numbers of megakaryocytes and granulocytic-erythrocytic ratios.

Thus our own observations and those in the literature during the extensive and protracted use of organomercurial drugs in recent years lead us to believe that, in therapeutic doses, they are among the safest and best-tolerated drugs. Accordingly, it seemed reasonable to explore, under closely controlled conditions, a technique using massive doses by intravenous infusion as an approach to the problem of patients refractory to the usual mercurial and other diuretic therapy. Without attempting to define the mechanisms involved in such re-

TABLE 1

BONE-MARROW BIOPSIES OF PATIENTS RECEIVING PARENTERAL MERCUHYDRIN*

Patient	Mg. Hg	Time in months	G/E† ratio	Megakaryocytes
J.P.	4460	28	85/15	Normal
S.P.	4480	44	85/15	Normal
Y.E.	4943	47	82/18	Normal
E.K.	2593	19	83/17	Normal
B.G.‡	8970	33	60/40	Normal
B.L.	2496	16	80/20	Normal
J.B.	4738	27	81/19	Normal

* Average dosage: 40 mg. Hg week for 25 months.
† Granulocytic-erythrocytic.
‡ Polycythemia vera.

sistance, it occurred to us that this increase in dosage and change in method of administration might break through the "mercury-fast" barrier.

This research involved a number of interrelated problems. First, of course, was the question of whether slow intravenous infusion would break through this barrier. Second, would the patient on long-term therapy be able to tolerate further large doses of the diuretic by this method of administration without any untoward or toxic effects on cardiac or renal status, or on bone-marrow, blood, or urine findings.

Fifteen hospitalized subjects were chosen for the intravenous studies. Three of them were controls who exhibited no clinical or laboratory evidence of cardiovascular renal disease or liver disease. The other 12 were patients with moderate to advanced edema due to long-standing hypertension or arteriosclerotic or rheumatic heart disease. These patients were selected on the basis of minimal renal pathology.

The edematous patients were "mercury-resistant" in that, despite daily injections for as long as 16 days, a good diuretic response, 2 to 3 times the normal urine output, could not be obtained with intramuscular Mercuhydrin or mercaptomeria sodium (Thiomerin). It has been reported that mercurial diuretics may be potentiated by Diamox, but in our cases there was no diuretic response to Diamox, either alone or in combination with the mercurials.

In our studies the average dietary sodium chloride intake was about 5.0 to 6.5 gm. day, and about 4 gm. of supplementary potassium chloride was given to compensate for any excessive potassium loss. Supplementary vitamins were also included in the patients' diets.

On the morning of the test, a urinary catheter was inserted, and the output of urine was measured for 1 hour. The diuretic was given in terms of milligrams of mercury per kilogram of body weight in 250 c.c. of 5 per cent glucose in water (TABLE 2). Mercuhydrin was used as a standard because of its wide acceptance and easily recognized behavior.

All subjects had repeated electrocardiogram (ECG) tracings (12 standard leads) almost continuously for the first 3 hours of the experiment, as follows: before the catheter was inserted, during the 1-hour period of catheter retention, and at intervals during the infusion of the diuretic and 5 per cent glucose solu-

TABLE 2

THE EFFECT OF INTRAVENOUS DIURETICS ON 24-HOUR URINE VOLUME

Patient	Urine volume in c.c./24 hr.	Diuretic and dose	Urine volume after diuretic c.c./24 hr.
P.S.	510	3.0 mg./kg. (M) –195–	2000
	530	3.2 mg./kg. (SU) –199–	3400
A.S.	730	3.2 mg./kg. (M) –156–	3850
	690	3.0 mg./kg. (SU) –148–	3600
W.G.	310	2.2 mg./kg. (M) –156–	2980
	270	2.5 gm. (D)	1570
G.M.	700	3.0 mg./kg. (M)	3470
	810	3.0 gm. (D)	2140
M.D.	530	2.5 mg./kg. (M) –166–	2350
	620	2.5 gm. (D)	1300
M.A.	730	2.4 mg./kg. (M) –158–	2900
	680	2.0 gm. (D)	1600
D.B.	720	2.2 mg./kg. (M) –148–	2270
		2.0 gm. (D)	1990
H.T.	520	1.5 mg./kg. (M) –127–	2660
	600	1.50 gm. (D)	1470
M.L.	1700	2.5 mg./kg. (M) –159–	2760
	1540	2.0 gm. (D)	1630
M.B.	1280	2.0 mg./kg. (M) –170–	3210
	1370	2.0 mg./kg. (SU) –170–	2650
T.T.	1400	2.3 mg./kg. (M) –134–	2650
	1310	2.3 mg./kg. (SU) –134–	2780
Y.S.	625	3.1 mg./kg. (M) –214–	3950
	640	3.2 mg./kg. (SU) –217–	3800
P.R.	570	3.3 mg./kg. (M) –229–	5600
	600	3.5 mg./kg. (SU) –241–	5400
R.D.	840	2.3 mg./kg. (M) –213–	3900
	810	2.3 mg./kg. (SU) –213–	4040
Z.G.	340	2.8 mg./kg. (M) –195–	2100
	290	2.6 mg./kg. (SU) –190–	1900

M = Mercuhydrin; D = Diamox; SU = SU-1775.

tion. ECG tracings were also made after the completion of the diuretic infusion at 20-min. intervals for 2 hours, and they were repeated at the end of the 4th, 6th, and 24th hours.

The infusion was administered at rates up to 8 c.c. min., and generally took from 70 to 100 minutes. Blood for chemical analysis was drawn just before the infusion, and again 6, 24, and 48 hours afterward, when it was examined for urea nitrogen, sodium chloride, and potassium and, occasionally, for carbon-dioxide combining power. The urine volumes were measured for an 8-hour period with the catheter *in situ*, and the volume and sodium and potassium per hour were determined. After the 8-hour period the catheter was withdrawn, and the urine was pooled for the next 16 hours.

After an interval of from 5 to 10 days, the procedure was repeated, using another diuretic on the same patient. Wherever possible, the weight of the patient was brought to the original level so that administration of the drug would not be influenced by previous states of dehydration or edema.

The data in TABLE 2 demonstrate the diuretic effects of the intravenous administration on the mercury-resistant patients. Intravenous Diamox in the cardiacs produced a 24-hour urinary output twice that of the control group, but SU-1775* and Mercuhydrin in these patients yielded a urinary output approximately 4 times that of the controls. Once compensation was achieved, these patients could be managed, depending on the individual case, with a low-salt diet, bed rest, and maintenance doses of parenteral mercurials.

As previously noted, the subjects were adequately supplied with sodium, potassium, and chloride in the diet, as well as vitamins. Comparatively small changes in the blood electrolytes were noted in all cases, as described in TABLE 3. In some patients, such as M. D., the urea nitrogen doubled, as was true of control patient M. B. but, in both cases, urea nitrogen remained within normal limits. There was no evidence of ECG changes, except in a single instance of diuretic-induced hypopotassemia. Potassium losses were marked in all cases but, even with these massive doses, only 1 patient lost sufficient potassium to produce clinical effects.

In only 2 cases did we note a reaction; namely, drowsiness, with Diamox, in patients M. A. and H. T. This appeared within one-half hour after the drug was administered.

Summary and Conclusions

"Mercurial fastness" was investigated in subjects exhibiting moderate to severe congestive heart failure who had developed resistance to mercurial diuretic therapy following long periods of satisfactory response to oral or parenteral administration of these agents.

It was found that when very large doses of Mercuhydrin or SU-1775 were administered by slow intravenous infusion, diuretic response was good. Urinary losses of electrolyte were always apparent. It is impressive to note that when a mercurial diuretic in an amount equivalent to as much as 3 mg. kg.

---

* SU-1775 is the code name of the experimental diuretic of CIBA Pharmaceutical Products, Inc., Summit, N. J.

TABLE 3
MASSIVE-DOSE INTRAVENOUS DIURETIC THERAPY

Patient	Blood Chemistry			24 hr. Urine vol	Urine vol./hr. with catheter	Diuretic dose intravenous	ECG changes	24 hr. postdiuretic		
	Urea N mg. %	Na mEq./l.	K mEq./l					Urea N mg. %	Na mEq./l.	K mEq./l.
Y.S.	15	134	3.9	620 c.c.	22 c.c.	(M) 3.1 mg./kg. Hg –214–	None	19	129	3.3
	Glucose-149 17	137	4.1	640 c.c.	20 c.c.	(SU) 3.2 mg./kg. Hg –217–	None	21	132	3.3
P.R.	19	136	4.1	570 c.c.	24 c.c.	(M) 3.3 mg./kg. Hg –229–	Compatible with hypopotassemia	23	134	3.0
	CO$_2$-59 vol. % 16	139	3.6	600 c.c.	26 c.c.	(SU) 3.5 mg./kg. Hg –241–	Compatible with hypopotassemia; arrhythmia?	16	138	4.2
R.D.	11 CO$_2$-63 vol. %	145	5.1	840 c.c.	36 c.c.	(M) 2.3 mg./kg. Hg –213–		15	134	3.6
	12	147	4.5	810 c.c.	33 c.c.	(SU) 2.3 mg./kg. Hg –213–	None	16	139	4.0
Z.G.	16	139 Cl-108	4.0	340 c.c.	19 c.c.	(M) 2.8 mg./kg. Hg –195–	None	16	140	3.8
	19.5	140	4.4	290 c.c.	20 c.c.	(SU) 2.6 mg./kg. Hg –190–	None	18	133	3.3
P.S.	17	134 Cl-97	3.8	510 c.c.	31 c.c.	(M) 3.0 mg./kg. Hg –195–	Hypopotassemia?	20	128	3.2
	15.8	132	4.1	530 c.c.	27 c.c.	(SU) 3.2 mg./kg. Hg –199–		15	129	3.4
A.S.	21 CO$_2$-61 vol. %	135	4.0	730 c.c.	39 c.c.	(M) 3.2 mg./kg. Hg –156–	None	18	130	3.7
	23	134	3.8	690 c.c.	38 c.c.	(SU) 3.0 mg./kg. Hg –148–	None	21	128	3.3
W.G.	17	139 Cl-94	4.2	310 c.c.	17 c.c.	(M) 2.2 mg./kg. Hg –156–	None	20	134	4.0
	16	135	4.2	270 c.c.	19 c.c.	(D) 2.5 gm.	None	17	135	3.3

Patient	Blood Chemistry			24 hr. Urine vol	Urine vol./hr. with catheter	Diuretic dose intravenous	ECG changes	24 hr. postdiuretic		
	Urea N mg. %	Na. mEq./l.	K mEq./l.					Urea N mg. %	Na mEq./l.	K mEq./l.
G.M.	19	132 Cl-90	3.7	700 c.c.	30 c.c.	(M) 3.0 mg./kg. Hg –214–	None	24	127	3.5
	20	136	4.7	810 c.c.	27 c.c.	(D) 3.0 gm.	None	19	131	3.2
M.D.	10	134	3.7	530 c.c.	26 c.c.	(M) 2.8 mg./kg. Hg –166–	None	23	128	3.1
	23	137	4.2	620 c.c.	24 c.c.	(D) 2.50 gm.	None	22	130	3.3
M.A.	11	141	5.3	730 c.c.	29 c.c.	(M) 2.4 mg./kg. Hg –158–	None	14	134	4.2
	12	143	4.9	680 c.c.	27 c.c.	(D) 2.0 gm.	None	—	132	4.1
D.B.	13	137	5.2	720 c.c.	34 c.c.	(M) 2.2 mg./kg. Hg –148–	None	13	135	3.9
	14	140	4.8	700 c.c.	33 c.c.	(D) 2.0 gm.	None	12	134	3.6
H.T.	20	134	4.6	520 c.c.	21 c.c.	(M) 1.5 mg./kg. Hg –127–	None	25	131	3.2
	14	140	4.5	600 c.c.	25 c.c.	(D) 1.5 gm.	None	22	134	3.6
M.L.*	14	143	4.6	1700 c.c.	61 c.c.	(M) 2.50 mg./kg. Hg –159–	None	16	141	3.7
	13	145	5.1	1540 c.c.	63 c.c.	(D) 2.0 gm.	None	14	—	4.4
M.B.*	11	142	4.9	1280 c.c.	57 c.c.	(M) 2.0 mg./kg. Hg –170–	None	11	141	3.9
	12	146	5.3	1370 c.c.	54 c.c.	(SU) 2.0 mg./kg. Hg –170–	None	24	137	3.8
T.T.*	16	146	5.0	1400 c.c.	51 c.c.	(M) 2.3 mg./kg. Hg –134–	None	15	141	3.9
	15	142	4.7	1310 c.c.	53 c.c.	(SU) 2.3 mg./kg. Hg –134–		17	136	—

M = Mercuhydrin; SU = SU-1775; D = Diamox; –214– = mg. Hg; (—) = not recorded.
* = a member of the control group.

was given by slow intravenous infusion, there was no apparent toxicity attributable to the compounds.

From this data it may be concluded that:

(1) Our own experience and the consensus expressed in the literature indicate that, in therapeutic doses, the mercurial diuretics can be used safely for long periods of time. The long-term administration of Mercuhydrin in quantities exceeding 2000 mg. of mercury per year for almost 4 years did not produce any untoward changes.

(2) Adequate diuretic response to massive doses of Mercuhydrin or SU-1775 given by slow intravenous infusion can be produced in moderate to severe congestive heart failure patients previously exhibiting "fastness" to oral or parenteral mercurial therapy. The carbonic anhydrase inhibitor, Diamox, will also produce a lesser diuretic response in the same patients when given in the same manner, the volume of diuresis being less than half that induced by the mercurial compounds. Both the mercurial diuretics and the carbonic anhydrase inhibitor bring about marked potassium losses when given by slow intravenous infusion.

(3) Neither cardiac changes, as reflected by physical examination and continuous ECG recordings, nor renal pathology, in terms of significant urea nitrogen differences, are produced by either the mercurial diuretics or the carbonic anhydrase inhibitor when administered by slow intravenous infusion.

Patients who have previously received large quantities of parenteral mercurial diuretics are apparently able to benefit from and tolerate, without detrimental effects, high dose levels of additional mercurial diuretics administered by slow intravenous infusion.

References

1. Burch, G. E., C. T. Ray, S. A. Threefoot, F. J. Kelly & A. Svedberg. 1950. Urinary excretion and biologic decay periods of radiomercury labelling a mercurial diuretic in normal and diseased man. J. Clin. Invest. **29:** 1131–1138.
2. Handley, C. A., D. Chapman & J. H. Moyer. 1951. Some pharmacological properties of three new mercurial diuretics. Proc. Soc. Exptl. Biol. Med. **78:** 433–437.
3. Pitts, R. F. 1955. The Pharmacology and Mechanism of Action of Mercurial Diuretics. Trans. Am. Chem. Soc. Div. Medicinal Chem. IV. Cincinnati, Ohio.
4. Griffith, G. C., E. M. Butt & J. Walker. 1954. The inorganic element content of certain human tissues. Ann. Internal Med. **41:** 501–509.
5. Leff, W. A., H. L. Nussbaum, V. D. Mattia, Jr. & E. C. Hillman, Jr. 1955. Oral chlormerodrin clinically effective without renal toxicity. Scientific Exhibit. 104th Ann. Meeting Am. Med. Assoc. Atlantic City, N. J.

REACTIONS TO THE ORGANOMERCURIAL COMPOUNDS

By Ethan Allan Brown
Allergy Section, Boston Dispensary Unit, New England Medical Center, Boston, Mass.

The allergist, who is a student of the untoward effects of drugs, should be interested in the reactions to mercurial diuretics for two reasons. One has to do with these drugs per se, the other concerns their exemplification of the increasingly important role of drug reactions in the management of chronic disease. These drugs and the salt-free diet account for the fact that so many of our patients with congestive heart failure are now alive.

With an aging population there will be more and more patients with congestive heart failure to treat. In addition, the very fact that these patients will now live longer on maintenance doses of mercurial agents raises the question of how well they will tolerate the necessarily prolonged treatment. We must therefore expect to meet the problems of individual sensitivity to these or alternative drugs more frequently.

Ideally, of course, we should possess a greater knowledge of the diuretic drugs than we now enjoy. For example, there is no series of data concerned with any one of these drugs sufficiently large to give us a statistically valid measure of the incidence of the various types of reactions. We have appealed elsewhere for epidemiological studies in which the total number of patients exposed to each drug could be related to the total number of reactions. Lacking this information, we can only analyze and interpret the literature composed, as it is, of small series that are invalid statistically, and of individual case reports that are ultimately the most unreliable sources of information in guiding us in the management of any individual patient.

In defense of these reports, both the small series and the individual cases, let it be said that all the variables involved in complex and chronic disease cannot be isolated readily. At the risk of redundancy, it should be stated again that we are dealing not with individual organs suspended from a skeleton but with the intricate interactions of the physiology and, perhaps, the pathology of a total patient.

In congestive heart failure and, indeed, in the whole problem of fluid and electrolyte balance, these interactions are marvelously subtle, and their unraveling challenges both our knowledge and our imagination. Although precision and controlled conditions are specifications easily prescribed, they are difficult to achieve.

Within these limits, we propose to discuss what we do know—and what we should like to know—about the reactions to mercurial diuretics.

The Patient or the Drug?

It is not easy to differentiate between the reactions presumably due to properties of the drug and those inherent in the patient or associated with the disorder. The problem is not made simpler by the fact that mercury is present in food, the normal daily diet containing approximately 20 μg. (Gibbs, Pond, and Hansmann[1] and T. Sollmann[2]). The amounts of mercury deposited in body tissues vary from organ to organ, and the amount retained by the body varies with each individual, an average mercury content being present in concentrations of 2.05 mg./100 gm. of dry kidney tissue as determined by spectrographic analyses of 910 autopsies (Griffith, Butt, and Walker[3]).

Forney and Harger[4] found concentrations up to 12.7 mg./100 gm. of kidney tissue present in 92 patients who had never been known to have been exposed to preparations of mercury. On the other hand, the studies of Griffith, Butt, and Walker[3] also showed that patients who had received an average total dose of 4692 mg. of mercury for periods ranging from 3 weeks to 40 months carried more mercury in their kidney tissue than did untreated patients, but that this was not associated with either renal disorders or rising nonprotein nitrogen levels of the blood. They concluded that "small *and* massive doses [of mercury diuretics] are not injurious in the absence of anuria due to hyponatremia."

Those few individuals who possess an idiosyncrasy to mercury will respond abnormally to its presence, either initially or after a sensitization process. In some cases this process will be quantitative as well as qualitative as, for example, when the mercury is introduced into the body more quickly than the tissues can cope with it. Speed of administration, alone, may cause levels of concentration that are toxic in themselves. This is true, however, of many drugs that, because of their basic properties, route of administration, and concentration in the tissues affect body tolerance.

It is important to realize that many of the fatalities formerly attributed to the injection of mercurial diuretics are, in the light of our present knowledge, known to be due to other causes. In 1948, Kaufman,[5] reviewing 23 years of published literature, found 32 reports of fatal cases. All of these fatalities followed intravenous therapy. Kaufman notes that "time relations, moribund condition of the patient, and other factors leave room for doubt about the role of the mercurial." Other reviewers, especially Ray and Burch,[6] observed further that large doses had been given to patients suffering from preexisting nephrosis and nephritis and, in some cases, previous intolerance to the drug had been demonstrated by these patients. Certainly, in the children of whom we have reports, the doses are now known to have been excessive. In 1948, Stanley[7] reported on 27 fatalities, 26 of which had been included in Kaufman's review.[5] In some of these cases, warnings had been present. In 1 patient, who had been given 4 injections with no ill effect, the fifth injection was followed by chills and fever and a morbilliform eruption. The sixth injection was followed by sudden death. In another patient, the penultimate injection caused apprehension and dyspnea, and the last injection caused death. Since, in many of these patients, death followed the use of types of mercurial compounds no longer administered today, these reports are of only historical interest. One conclusion is possible, however, and that is that it does not matter how often a patient has taken the drug safely. When there is a rise in temperature and a rash, the presence of a sensitization process can be postulated.

In these cases, one may say with some assurance that very often the patient and *not* the drug is at fault. Similarly, Tepley's[8] advice that "over-enthusiastic efforts to rid the body of sodium may result in serious and perhaps fatal electrolyte depletion" should be remembered. Krantz and Carr[9] also wisely point out that many of the symptoms attributed to the diuretic agents reflect problems in management of the patient.

Method of Administration

If many of the reactions reported were due to intravenous administration—that is to say if the injections were made at so rapid a rate that the body could not tolerate the drug—then the problem of the method of administration is an important part of the study of reactions to organomercurial agents. The fact that the reactions occurred with intravenous injection does not mean that the same drug can always safely be used intramuscularly or subcutaneously. Occasionally, an unfavorable reaction to the intravenous administration may be followed by an equally or more serious reaction when the drug is administered intramuscularly.

Is it the Dose?

Since the reactions may be due to the amount of the drug taken, we cannot accept the use of 1 to 2 ml. as a "standard dose." Dicker[10] emphasizes the fact that "the dose must be calculated on the basis of mg./kg."

Since the physician is not always in a position to judge when the dose and the time interval are part of a sensitization process, it would be wise to test the patient first with a small dose of an oral preparation. It is commonly true that a small dose of many medicinal agents "conditions" the cells so that they can tolerate much larger doses later. This process has been shown to be valid for both animals and man.

Are the Drugs all the Same?

It should be noted that all reported reactions to all mercurial preparations are lumped together, irrespective of the date, the dose, or the method of administration. It is important for us to be absolutely clear regarding the fact that the new drugs are quite different from the old drugs, and that the currently used compounds differ from each other. The literature concerned with the mercurials is an example of how a misapprehension, born of a long history, can persist in the face of facts to the contrary. The erroneous concept does not differentiate among the many forms of mercury or the varying routes of administration. Old and new drugs with remarkably different properties are grouped together indiscriminately. Slight chemical changes cause marked therapeutic variations, however. It has been pointed out by Fourneau and Melville[11] that the activity of the newer mercurial agents is not related directly to the amount of mercury these agents contain, but to their chemical linkage.

In a comparison of 6 preparations adjusted to a mercury content of 40 mg./cu. mm., DeGraff and Lehman[12] noted marked differences in diuretic activity. In animals, chlormerodrin (Neohydrin), given intravenously, is 3 to 4 times more active than meralluride sodium solution (Mercuhydrin), and the rates of excretion of both Neohydrin and Mercuhydrin are greater than those of mercaptomerin sodium (Thiomerin) (Handley, Chapman, and Moyer[13]). As we know, the newer materials act selectively and demonstrably at different sites of the tubule (Mustakallio and Telkkä[14]), which again serves to emphasize the fact that mercurial diuretics are not "all the same." Not only must the newer organomercurial agents not be confused with the older ones but, in terms of sensitivity reactions, they often differ sufficiently among themselves to make it relatively safe to go from one to another.

For example, Segal[15] reported on a 51-year-old white male who suffered from cardiac decompensation due to rheumatic heart disease. The patient reacted to Thiomerin with abdominal cramps, vomiting, and the appearance of large, discrete, erythematous patches on the arms, legs, back, penis, and gluteal areas. The same reaction reappeared following 3 subsequent injections of the same diuretic. This reaction was not seen, however—and this is the point—after treatment with other mercurial diuretics. Of interest in this special case is the fact that hematological studies performed after the second injection of Thiomerin disclosed a marked reduction of blood platelets (70,000) and a marked prolongation of clot retraction. This is evidently the first report of a hematological response of this type following treatment with a mercurial diuretic agent.

The Nature of the Reaction

Since I have commented elsewhere (Brown[16]) on the reactions to mercury as such and the relation of these reactions to the signs and symptoms of mercurialism seen following ingestion of the inorganic salts of mercury, such as bichloride of mercury, I need not do so here.

This fear of "mercurialism," however, may account for the fact that the literature on organomercurial compounds contains case reports not seen in any other aspect of therapeutics. No one troubles to stress the amount of penicillin a patient has taken with safety, yet physicians reporting on organomercurials note either the total dose or the length of time during which their patients took the newer mercurial compounds. One of my patients took weekly injections for more than 10 years. There are published records of patients who have taken as many as 627 injections over a period of 12 years (Friedenson[17]). Another patient is reported as having received 343 injections over a period of 7½ years. DeGraff and Nadler[18] have noted that at Bellevue Hospital, New York, N.Y., 6000 injections of mercurial diuretics were given yearly for 8 years with no serious toxic reaction or any death that might be attributed to these drugs. It is reported that 13,000 injections administered over a period of 4 years caused no untoward effects (Leevy and White[19]).

The occurrence of pain and other local reactions has been assessed carefully by a number of workers. Double-blind tests have established the fact that the injection of Mercuhydrin is less painful than mercurophylline (Mercupurin) injection. Both of these drugs appear to cause less discomfort than does Thiomerin. The order of magnitude of such reactions may vary from none, as reported by Sussman and Stein,[20] who found no local reactions following 1000 injections of Mercuhydrin, given subcutaneously, to as much as 44 per cent in a group of patients given Thiomerin by Gold and his associates.[21] This matter is not one of major importance, and its significance may depend entirely upon technique.

Some of the oral reactions supposedly following the use of mercurial diuretics can be dismissed since, at least in the present state of our knowledge, it is established that they are associated with the state of the bacterial flora of the oral cavity and, probably, upon oral hygiene. Occasionally they are due to electrolyte imbalance. The correction of all 3 factors would certainly reduce markedly the number of patients responding in this manner.

The gastrointestinal symptoms supposedly following the use of mercurial agents are difficult to evaluate. Cramps and nausea have been reported as following intravenous, intramuscular, and subcutaneous injections. Some of these symptoms may be due to concomitant therapy, as with digitalis, and be due to relative overdigitalization following hemoconcentration. With the oral diuretic agents, the gastrointestinal symptoms may disappear as the drug is continued or if the administration is initiated with small doses. The number of patients reacting in this manner is small. If such symptoms persist with a change of diuretic agent, the initiation of the sensitization process may well be suspected.

Dermatological reactions are always signs of sensitization. They may begin with marked pruritus and progress to urticaria. Occasionally the patient may present morbilliform or purpuric eruptions and, rarely, exfoliative dermatitis. The skin reactions may occur alone, or they may be accompanied or followed by chills, fever, and asthma. In the early stages these reactions may be innocuous and reversible but, no matter how mild they may be, they are always warnings that must not be ignored. In some patients the skin reactions lessen with successive treatments, proving that a desensitization process or tolerance is developing. When they do occur with each administration and grow more intense each time, however, the drug should be discontinued.

As regards kidney effects, it is surprising that there is so little mention of renal reactions. Bruno[23] says that much accumulated evidence indicates that patients with renal impairment respond well to mercurial diuretics, and Goldring[24] remarks that there may be reason to believe that the impaired but functioning kidney is less liable to injury since its inability to concentrate will result in a more dilute solution of mercury in its tubular fluid. The so-called "cardiovascular reaction" occurred most often with the older mercurials given intravenously. Bone-marrow effects have occurred but rarely, and the blood dyscrasias described are undoubtedly due to specific sensitivity. In the 2 cases reported, recovery followed treatment with British anti-lewisite (BAL). The possibility of the occurrence of specific sensitivity must always be kept in mind.

What has come to be known as the "systemic reaction", associated with chills, fever, palpitations, tachycardia, cardiac arrhythmias, fall in blood pressure, dizziness, and vomiting may be allergic in nature. It usually occurs in patients who have taken treatment for prolonged periods of time. In a number of these patients a substitution of one for another type of mercurial diuretic may suffice to prevent further complications.

It appears that some patients exhibit a sensitivity to the organic compound and not to the mercury and, in others, to the mercury in one conjugate, but not to the mercury in another conjugate. Cross-sensitization, however, is sometimes seen. The patient studied by Fox, Gold, and Leon[22] responded to an intravenous injection of Mercupurin with labial angioedema, conjunctival infection, a diffuse erythematous eruption, and a rise in temperature to 103° F. Although there was a variation in the degree of reaction, other organic mercurial diuretic compounds caused the same response. In similar cases the chemical relationships between the drugs should be studied and, if mercurial diuretics must be used, those most unlike each other may be administered cautiously.

True sensitivity is best proved by reverse passive-transfer techniques with posttreatment serum. Normal serum and that taken from a patient being treated with the mercurial in question are separately injected, intradermally, into the patient in whom sensitivity is suspected. A positive test with the serum of the donor who has been treated with a mercurial proves the presence of both the antigenic activity of the serum and the sensitivity of the recipient.

When is a Reaction not a Reaction?

Any discussion of reactions to mercurial diuretic agents must emphasize the fact that many so-called reactions are not reactions; rather, they are the results of excessive diuresis, causing sodium and potassium deficiencies. These results may be due to hemoconcentration or digitalis toxicity, or they may be related to loss of calcium, vitamin deficiency, and the effects of serious dehydration.

One patient whom I observed was suffering from salt depletion, and presented restlessness, abdominal cramps without diarrhea, tachycardia, nausea, lassitude, and coma. The patient recovered within minutes after the injection of hypertonic saline.

Hypokalemia may follow or accompany hyponatremia. High potassium salt intake is effective immediately. Usually these patients use their potassium efficiently, and hypokalemia is rare.

With hemoconcentration there may be phlebothrombosis, coronary cerebral artery thrombosis, or pulmonary embolism.

The 3 common errors of judgment are: first, the use of mercurial diuretics in the presence of *acute* glomerulonephritis and, second, their use in *chronic* renal disease. The third error is the most important: if there is no response from mercurial diuretics, something is radically wrong, and it must be corrected before the drug in the same or a larger dose is again administered.

At the risk of appearing to moralize, I should suggest that it is not the best medical practice to withhold an effective drug because we do not possess exact knowledge of *all* of its properties. It is not the best medical practice to use, instead, an ineffective drug because we mistakenly think that it is "safe."

We say "mistakenly" advisedly, because there is no such thing as a safe drug, although innocuous drugs may seem to involve fewer hazards. This is true only because we neglect to include the hazards from the inadequately treated disease itself. In any case, we do not have the information that enables us to predict, for example, except under very special circumstances, which patient will react to penicillin with an anaphylactic shock or, for that matter, to acetylsalicylic acid with a fatal idiosyncratic reaction.

It is therefore the problem of the student of drug reactions to study potent agents such as the mercurial diuretics and to interpret, as well as our present knowledge permits, the facts that will guide us in their use. For the researcher, the problem is to uncover and report information that will help us to designate that larger group of patients for whom these potent drugs are indicated, and to locate that smaller group for which they are contraindicated. Our reluctant use of less effective drugs could then be confined to this smaller group. Such medical practice redefines the term "conservative treatment" in this era of potent therapeutic agents.

In conclusion, it would appear that the organomercurials are remarkably safe drugs when used correctly. Their administration, however, requires recognition of the fact that in every patient who requires them there is an interplay of a number of pathological processes and physiological mechanisms. All of these must be taken into consideration. There are few fields of medicine in which the physician requires greater judgment. On the other hand, there are few disorders of the type requiring treatment with mercurial diuretics where the results can be so immediate, so apparent, and so satisfactory.

References

1. Gibbs, O. S., H. Pond & G. A. Hansmann. 1941. Toxicological studies on ammoniated mercury. J. Pharmacol. Exptl. Therap. **72:** 16.
2. Sollmann, T. 1942. A Manual of Pharmacology. Saunders. Philadelphia, Pa.
3. Griffith, G., E. M. Butt & J. Walker. 1954. The inorganic element content of certain human tissues. Ann. Internal Med. **41:** 501.
4. Forney, R. B. & R. N. Harger. 1949. Mercury content of human tissues from routine autopsy material. Federation Proc. **8:** 292.
5. Kaufman, R. E. 1948. Immediate fatalities after intravenous mercurial diuretics. Ann. Internal Med. **28:** 1040.
6. Ray, C. T. & G. E. Burch. 1949. The mercurial diuretics. Am. J. Med. Sci. **217:** 96.
7. Stanley, T. E. 1949. An analysis of 27 reported fatalities immediately following the injection of a mercurial diuretic. Virginia Med. Monthly **8:** 416.
8. Tepley, F. H. 1952. Dangers of salt depletion in heart failure. GP. **5:** 53.
9. Krantz, J. D., Jr. & C. J. Carr. 1954. The pharmacologic principles of medical practice. Williams & Wilkins. Baltimore, Md.
10. Dicker, S. E. 1951. Diuretics and diuresis. J. Pharm. and Pharmacol. **3:** 449.
11. Fourneau, E. & K. Melville. 1931. Studies in mercurial chemotherapy. 1. Concerning mercurial toxicity, its evaluation, mechanism, and relation to chemical constituents. J. Pharmacol. Exptl. Therap. **41:** 21.
12. DeGraff, A. C. & R. A. Lehman. 1942. The acute toxicity of mercurial diuretics. J. Am. Med. Assoc. **119:** 998.
13. Handley, C. A., D. Chapman & J. H. Moyer. 1951. Some pharmacological properties of three new mercurial diuretics. Proc. Soc. Exptl. Biol. Med. **78:** 433.
14. Mustakallio, K. K. & A. Telkkä. 1955. Selective inhibition patterns of succinic dehydrogenase and local necrobiosis in tubules of rat kidney induced by six mercurial diuretics. Ann. Med. Exptl. et Biol. Fenniae (Helsinki). Suppl. **1:** 1.
15. Segal, R. L. 1955. Toxic reaction to Thiomerin. Ann. Internal Med. **43:** 435.
16. Brown, E. A. 1955. The question of reactions to mercurial diuretics. Ann. Allergy. **13:** 131.

17. Friedenson, M. 1944. The prolonged use of mercurial diuretics in heart failure. Ann. Internal Med. **20:** 306.
18. DeGraff, A. C. & J. E. Nadler. 1942. A review of the toxic manifestations of mercurial diuretics in man. J. Am. Med. Assoc. **119:** 1006.
19. Leevy, C. M. & T. J. White. 1951. Diuresis in congestive heart failure. J. Med. Soc. New Jersey. **48:** 12.
20. Sussman, R. M. & J. J. Stein. 1950. Successful subcutaneous injections of a mercurial diuretic. N. Y. State J. Med. **50:** 987.
21. Gold, H., T. Greiner, S. B. Mathes, R. R. Marsh, L. J. Warshaw, W. Modell, N. T. Kwit, H. L. Otto, S. Garb, H. Bakst & M. L. Kramer. 1952. Study of the mercurial diuretic, Thiomerin (mercaptomerin) by subcutaneous injection in patients with congestive failure, with special reference to local reactions. Am. J. Med. Sci. **223:** 618.
22. Fox, T., H. Gold & J. Leon. 1942. Hypersensitiveness to a mercurial diuretic. J. Am. Med. Assoc. **119:** 1497.
23. Bruno, M. S. 1948. Fatal toxic nephrosis following the administration of mercurial diuretics. New Engl. J. Med. **239:** 769.
24. Goldring, W. 1946. Cornell conferences on therapy; the use of the mercurial diuretics. N. Y. State J. Med. **46:** 62.

DISCUSSION: PART II

Carroll A. Handley, Chairman

Baylor University College of Medicine, Houston, Texas

Robert Pitts (*Cornell University Medical College, New York, N. Y.*): I should like to comment on Moyer's paper.

It has been suspected in the past, I think, that a mercurial diuretic acts as a molecule, and not by liberating ionic mercury. This became fairly evident from polarographic studies of excretion products performed by Müller and Weiner,[1] and it is now very definitely confirmed in these experiments of Moyer and his colleagues.

Reference

1. Müller, O. H. & I. M. Weiner. 1955. A polarographic study of mersalyl (Salyrgan)-thiol complexes and of the excreted products of mersalyl. J. Pharmacol. Exptl. Therap. **113:** 241–249.

Otto H. Müller (*State University of New York, Upstate Medical Center, Syracuse, N. Y.*): I should like to cite the conclusions based on some experiments that we have carried out on both Neohydrin and Salyrgan. If Salyrgan is administered *intravenously* to dogs, the excretion product is found to be, initially, a complex in which a cysteinelike substance is hinged onto the mercurial, Salyrgan. After 2 or 3 periods of collection, the excretion product changes into a Salyrgan complex with *acetylated* cysteine. We suspect that the first product is formed in the kidney and that the later acetylated product is formed in the liver.

When we give Neohydrin *by mouth*, it is never excreted as a cysteine complex of Neohydrin, but always as the *acetylated* cysteine complex of Neohydrin. This again points to the role of the liver in the formation of the detoxification product.

If we give Neohydrin *intravenously*, we never obtain an excretion of an acetylated cysteine-Neohydrin complex. In this case we get the cysteinelike complex for as long as 3 hours after the injection. Apparently the diuretic is excreted directly from the kidney, where it is stored, as Pitts and his collaborators have shown, and it therefore never has a chance to recirculate through the liver.

In confirmation of our suspicion of the role of the liver in this situation, we found that, after infusion of either Neohydrin or Salyrgan directly into the portal circulation, the excreted material seems identical with the complex of *acetylated* cysteine with the mercurial.

Robert A. Lehman (*Campbell Pharmaceutical Company, New York, N. Y.*): Since it seems evident that a considerable part of any of the mercurial diuretics is excreted in the form of mercaptide, either derived from fragments broken off from the intact mercurial or derived directly therefrom, is it not possible that a mercaptide obtained from a carboxyl-bearing thiol compound might be confused with the original mercurial, since it also has a carboxyl group?

Carroll A. Handley: We do not know at the moment just what these two fractions are. Probably the largest fraction represents a single component. At least, paper chromatography indicates that this is a single compound.

We do know that this fragment represents a compound with a carboxyl group, as in the original Mercuhydrin molecule. It could be a cysteine complex. It is possible that theophylline is removed from the parent compound which, in turn, may react with cysteine. We have not characterized it at the moment.

Jacob Grossman (*Montefiore Hospital, New York, N. Y.*): Moyer has indicated that much mercury is excreted prior to diuresis, as well as after the diuresis has subsided. It occurred to me that the degradation products might be defined better by making use of progressively smaller doses of mercurial until one approaches the minimum effective diuretic dose and noting, at that point, whether the breakdown products, as you separate them, are altered percentagewise. This might result in a significant difference in the ratio of degradation products.

John Moyer (*Baylor University College of Medicine, Houston, Texas*): It would not be practicable to reduce the dose of meralluride below an equivalent of 20 mg. of mercury. You get no measurable diuresis with smaller doses and, for all practical purposes, the relationship that you are seeking would be completely obscured. We have given doses of this size (20 mg. Hg) to normal subjects and patients in mild heart failure, and we have found that the amount of mercury excreted as degradation products continues to be less than 5 per cent of the meralluride mercury administered. The amount of mercury excreted as degradation product at this 20 mg. Hg dose ($\frac{1}{2}$ c.c.) is already so small that further reduction of dosage would reduce the degradation product to an insignificant amount, the measurement of which falls within the range of error of the methods employed for chemical analysis.

Carroll A. Handley: I should like to emphasize that diuresis must be due to the fraction retained by the column because, during some periods of diuresis, no degradation products are excreted. Therefore, diuresis must be due to whatever compound is retained by the column.

Robert Pitts: There is another interesting point, frequently discussed, for which I think we can provide an answer as a result of our work; namely, the question of how the mercurial compound that serves as a diuretic gains entrance to the renal tubules.

Is it reabsorbed from the glomerular filtrate, or is it taken up from the peritubular blood? From our studies of the binding of chlormerodrin to plasma protein, its rate of glomerular filtration, and its renal extraction, we can say definitely that the uptake of over 90 per cent of the mercurial by the renal tubules must be from the peritubular blood. In other words, the mercurial enters the renal tubular cell from its vascular border, not from the glomerular filtrate.

M. Wachstein (*St. Catherine's Hospital, Brooklyn, N. Y.*): The histochemical demonstration for succinic dehydrogenase activity has been used for studying the sites of action of mercurial diuretics. In the normal rat kidney, the tubules in the cortex and outer medulla show enzymatic activity. The terminal portions of the proximal convoluted tubules located in the outer medulla can be distinguished from the ascending limbs of Henle's loops, since the latter show a much more intense staining reaction. In our own experiments mercurial diuretics inhibited succinic dehydrogenase activity only in the terminal portions of the proximal convoluted tubules, regardless of whether meralluride or mercurophylline was used. This inhibition occurred only with doses that induced necrosis of tubular cells.[1, 2]

Our own results do not agree with the findings of Mustakallio and Telkkä.[3] These workers found that different segments of the proximal convoluted tubules were influenced by various mercurial diuretics, and that, with mercurophylline, inhibition of succinic dehydrogenase activity occurred in the ascending limbs of Henle's loops.

References

1. Wachstein, M. & E. Meisel. 1954. On the histochemical localization of the mercurial inhibition of succinic dehydrogenase in rat kidney. Science. **119:** 100.
2. Wachstein, M. & E. Meisel. 1954. Renal succinic dehydrogenase and mercurial diuretics. Experientia. **10:** 495.
3. Mustakallio, K. K. & A. Telkkä. 1955. Selective inhibition patterns of succinic dehydrogenase and local necrobiosis in tubules of rat kidney induced by six mercurial diuretics. Ann. Med. Exptl. et Biol. Fenniae. (Helsinki) Suppl. **1:** 1.

Alfred Farah (*State University of New York, Upstate Medical Center, Syracuse, N. Y.*): Previous attempts to define the cellular site of action of mercurial diuretics in the kidney have resulted in conflicting theories. Duggan and Pitts[1] postulated that the distal convoluted tubule was the site of action. On the other hand, the data of Mudge, Foulks, and Gilman[2] indicated an action on the proximal convoluted tubule. Farah and Koda[3, 4] concluded that no one site of action could explain all the phenomena occurring during a mercurial diuresis, and therefore postulated at least 2 sites of action. All of the above hypotheses have been based on results obtained by means of the classical clearance methods, and it was considered unlikely that such studies could distinguish clearly between various renal sites of action of a drug. We have therefore attempted to apply quantitative histochemical techniques to the problem of localizing the cellular site of action of mercurial diuretics.* Previous attempts with histochemical techniques by Mustakallio and Telkkä,[5, 6] Wachstein and Meisel,[7, 8] and Rennels and Ruskin[9] have resulted in conflicting conclusions. All of these groups of investigators used a tetrazolium method for determining succinoxidase activity in renal sections; it was felt that such methods were not sufficiently quantitative to permit a careful analysis of the data.

A summary of the evidence indicating that mercury may act by binding sulfhydryl groups has been presented previously.[10] This possible relationship between mercurials and sulfhydryl groups prompted Cafruny, Di Stefano, and Farah[11] to modify the method of Barrnett and Seligman[12] for protein-bound sulfhydryl and to adapt it for cytophotometric determination.

---

* This work was supported by a grant-in-aid from the U. S. Atomic Energy Commission, Washington, D.C., Contract No. AT(30-1)1737.

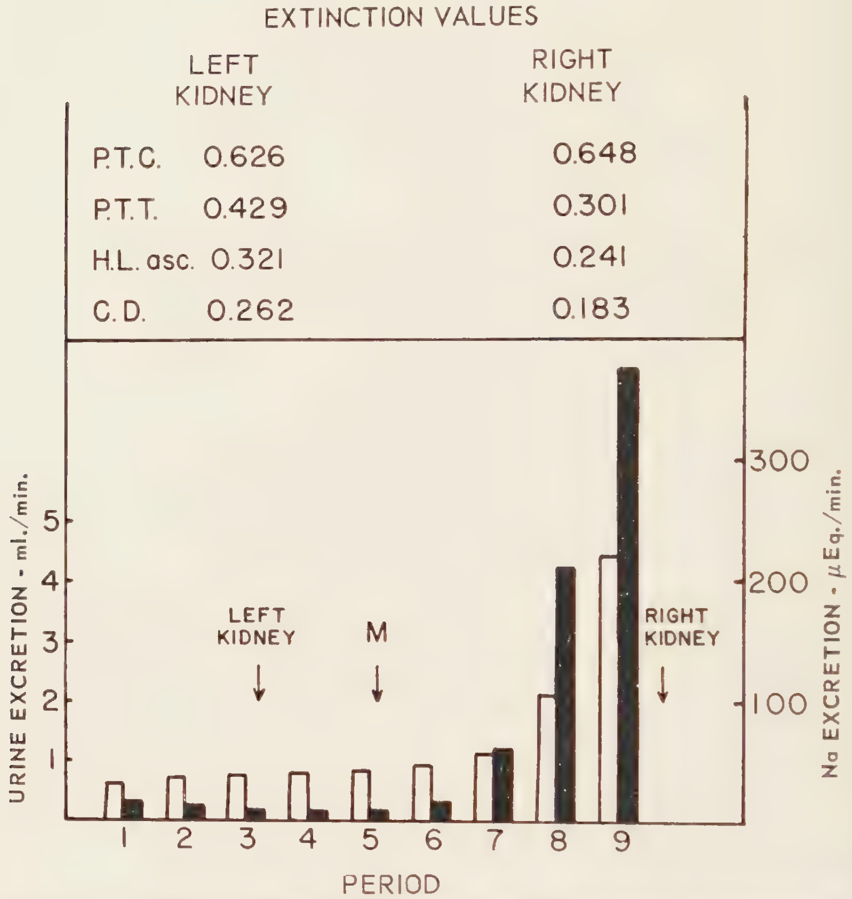


Figure 1. The effect of mersalyl on diuresis and on the protein bound sulfhydryl in the cytoplasm of the kidney cells of the dog. The subject is a female dog weighing 14.7 kg., under pentobarbital anesthesia, and receiving an infusion of isotonic saline at the rate of 3.0 ml./min.

At left kidney; left kidney removed.

At M; 10 mg./kg. mersalyl, administered intravenously.

At right kidney; right kidney removed.

Light columns; urine flow per minute.

Dark columns; sodium excretion per minute.

Each period equals 15 minutes.

The extinction values for protein bound sulfhydryl were determined cytophotometrically in renal cellular cytoplasm, using an apparatus similar to that described by Pollister and Moses.[14]

P.T.C. = proximal tubule, convoluted part; P.T.T. = proximal tubule, terminal part; H. L. asc. = ascending limb of Henle; and C.D. = collecting ducts.

A decrease in the extinction values denotes a decrease in protein-bound sulfhydryl concentration.

The effects of the mercurial on the cytoplasmic concentrations of protein-bound sulfhydryl in the cytoplasm of renal cells of the rat have been studied by Cafruny, Farah, and Di Stefano.[9] The data show that mersalyl produced a reduction in cytoplasmic protein-bound sulfhydryl in the cells of the terminal part of the proximal tubule, in Henle's loop, and in the collecting ducts. Cells of the convoluted part of the proximal tubule and the distal convoluted tubule did not show any reduction in protein-bound sulfhydryl.

In the above experiments we could not correlate the functional with the histochemical effects of the mercurials. This has now been accomplished in dogs, and details of these studies will appear in the near future.[13] FIGURE 1 is an example of the results of one of these experiments; there it can be seen that, concomitant with the mercury-induced increases in water and sodium excretion, there was a reduction in the protein-bound sulfhydryl in cells of the terminal part of the proximal convoluted tubules, in the cells of Henle's loop, and in the collecting ducts. No change could be detected in the cells of the convoluted parts of the proximal and distal convoluted tubules. British anti-lewisite (BAL), when given at the height of the mercurial diuresis, reversed both the pharmacological and the histochemical effects of the mercurial diuretic (TABLE 1). Furthermore, the administration of such monothiols as cysteine or glutathione reversed neither the mercury-induced diuresis nor the histochemical changes in the kidney cells of the dog.

It is known that acidosis potentiates, while alkalosis depresses, a mercurial diuresis. Anesthetized dogs were made acidotic or alkalotic by means of infusions of solutions of dilute hydrochloric acid or sodium bicarbonate. The control left kidney was removed and fixed in trichloracetic acid. This procedure was followed by the intravenous injection of 10 mg./kg. of mersalyl. Following the development of maximum diuresis, the right kidney was removed

TABLE 1

THE EFFECT OF MERSALYL AND BAL ON SULFHYDRYL CONCENTRATION IN THE CYTOPLASM OF KIDNEY CELLS OF THE DOG

	Extinction					Urine flow ml./min./M²	Sodium excretion mEq./min./M²
	Proximal tubules (convoluted portions)	Proximal tubules (terminal portions)	Loops of Henle (ascending limbs)	Distal tubules	Collecting ducts (inner medulla)		
Controls	.537 ± .003	.410 ± .004	.360 ± .015	.495 ± .004	.242 ± .004	0.83	0.17
Mersalyl (10 mg./kg.)	.541 ± .006	.267 ± .008	.261 ± .012	.510 ± .003	.192 ± .006	4.82	0.81
Mersalyl (10 mg./kg.) + BAL (10 mg./kg.)	.532 ± .007	.397 ± .004	.353 ± .007	.509 ± .008	.247 ± .005	0.94	0.10

TABLE 2

THE EFFECT OF MERSALYL ON PROTEIN-BOUND SULFHYDRL CONCENTRATIONS OF KIDNEY CELLS OF THE DOG DURING ACIDOSIS AND ALKALOSIS*

	Number of kidneys	Proximal tubule, terminal part	Collecting ducts (medulla)	Maximum increment after mersalyl	
				Urine flow ml./min.	Sodium excretion mEq./min.
Acidosis (control)	3	.412	.239	—	—
Acidosis ± Hg	3	.298	.179	3.8	455
Alkalosis (control)	3	.402	.138	—	—
Alkalosis ± Hg	3	.370	.214	1.3	186

* All values are extinction values determined cytophotometrically. The method used for staining protein-bound sulfhydryl was a modification of the method of Barrnett and Seligman[12] as modified by Cafruny, Di Stefano, and Farah.[11] The values are the averages of 3 dogs in each group.

and fixed in the same manner as the left kidney. The sections from control and experimental kidneys were stained for protein-bound sulfhydryl, and the extinction values for various types of renal cells were determined.

Preliminary results are given in TABLE 2. It can be seen that, in the acidotic dogs, the injection of mersalyl produced a marked diuresis, and that it also produced a marked reduction in the protein-bound sulfhydryl of the cells of the terminal part of the proximal tubules. In the alkalotic dogs, the diuresis and natriuresis, as well as the sulfhydryl reduction, were much less marked. Here, again, we have a correlation between the histochemical and pharmacological changes. The effects of mersalyl on the cells of the collecting ducts was quantitatively different in acidotic and alkalotic dogs. In the acidotic group, the mercurial produced a reduction of the protein-bound sulfhydryl in the cells of the collecting tubules, and this finding was similar to that observed in the normal animals (TABLE 1). In alkalotic dogs the protein-bound sulfhydryl was relatively low in the collecting-tubule cells of the control kidney, and in this case the injection of mersalyl increased the protein-bound sulfhydryl of these cells. This paradoxical behavior has been observed in all the dogs studied, as well as in alkalotic rats. At this time we are unable to suggest the functional significance of this observation.

The data presented suggest the possibility that the inhibition of protein-bound sulfhydryl in specific renal cells may be related to the diuresis produced by the mercurial. However, more experimental work will be needed before such a hypothesis can be accepted.

References

1. DUGGAN, J. J. & R. F. PITTS. 1950. Studies on diuretics. 1. The site of action of mercurial diuretics. J. Clin. Invest. **29:** 365–371.
2. MUDGE, G. H., J. FOULKS & A. GILMAN. 1949. Effect of urea diuresis on renal excretion of electrolytes. Am. J. Physiol. **158:** 218–230.
3. FARAH, A. & F. KODA. 1954. The influence of plasma electrolyte concentration on mercurial diuresis in the dog. J. Pharmacol. Exptl. Therap. **110:** 361–368.
4. FARAH, A. & F. KODA. 1955. The action of mercurial diuretics on urinary sodium concentration and urine volume. J. Pharmacol. Exptl. Therap. **113:** 256–261.
5. MUSTAKALLIO, K. K. & A. TELKKÄ. 1953. Histochemical localization of the mercurial inhibition of succinic dehydrogenase in rat kidney. Science. **118:** 320–321.

6. Telkkä, A. & K. K. Mustakallio. 1955. Proximal or distal mercurial inhibition of succinic dehydrogenase in the kidney tubules of rat. Science. **121:** 146.
7. Wachstein, M. & E. Meisel. 1954. On the histochemical localization of the mercurial inhibition of succinic dehydrogenase in rat kidney. Science. **119:** 100.
8. Wachstein, M. & E. Meisel. 1954. Renal succinic dehydrogenase and mercurial diuretics. Experientia. **10:** 495.
9. Rennels, E. G. & A. Ruskin. 1954. Histochemical changes in succinic dehydrogenase activity in rat kidney following administration of mercurial diuretics. Proc. Soc. Exptl. Biol. Med. **85:** 309–314.
10. Cafruny, E. J., A. Farah & H. S. Di Stefano. 1955. Effects of the mercurial diuretic mersalyl on protein-bound sulfhydryl groups in the cytoplasm of rat kidney cells. J. Pharmacol. Exptl. Therap. **115:** 390–401.
11. Cafruny, E. J., H. S. Di Stefano & A. Farah. 1955. Cytophotometric demonstration of protein-bound sulfhydryl groups. J. Histochem. & Cytochem. **3:** 354–359.
12. Barrnett, R. J. & A. M. Seligman. 1952. Histochemical demonstration of protein bound sulfhydryl groups. Science. **116:** 323–327.
13. Cafruny, E. J. & A. Farah. 1956. J. Pharmacol. Exptl. Therap. In press.
14. Pollister, A. W. & M. J. Moses. 1949. A simplified apparatus for photometric analysis and photomicrography. J. Gen. Physiol. **32:** 567–577.

James Fitzsimmons (*Taunton, Mass.*): Between 1947 and 1950, Frank Kozelka of the University of Wisconsin Medical School and I made several studies of the effect of BAL on the tissue distribution and excretion of mercury. We were concerned with the question of whether BAL increases the rate of excretion of mercury, an action that has been attributed to it.

We gave 2 groups of laboratory animals, monkeys and rats, sublethal doses of bichloride of mercury by various routes of administration. One group of rats was then given a clinical course of BAL, as outlined by Sollmann,[1] while the other served as a control.

When these animals were sacrificed and their tissues analyzed by a sensitive quantitative method, we found consistently that the control animal had a relatively higher kidney concentration of mercury than the BAL-treated animal. The control animal also revealed a significantly lower liver concentration of as little as half as much mercury as the treated animal. The carcasses of the BAL-treated animals were also analyzed and compared to those of the control animals. A much greater amount of mercury—up to a third again as much—was retained in the entire carcass of the treated animal than in that of the control.

This finding is hardly consistent with the concept that BAL increases the excretion of mercury. In another experiment, reported in 1949, animals were placed in metabolism cages, and their feces and urine were collected and analyzed. Mercury excretion was less in the BAL-treated animal than in the control animal.

These studies gave us every reason to believe that BAL does not increase the excretion of mercury, but that it forms in the tissues of the body a relatively inert, stable complex with mercury, which is slowly excretable.

Another study that we have not reported was designed to show the correlation between the dissociation of mercurial compounds and their toxicity. The purpose of this work was to determine by analytical methods, *in vitro*, the amount of mercury that is available to combine with a specific reagent, dithizon, and to discover if any correlation exists between the amount of mercury so available and the toxicity of the compound being tested, as determined by animal studies.

Assuming that the mercury in a compound reacts with dithizon at the *p*H of the body, it could also react with tissue or cell protein. This test, then, might be an index of toxicity.

For this experiment, samples of 12 experimental diuretics and of Mercuhydrin were provided by the Lakeside Laboratories, Inc., Milwaukee, Wis. The only data furnished on these experimental drugs were the code number of each and the percentage of mercury it contained.

These organic mercurial compounds were put into a buffered solution at the *p*H of tissue fluid. Mercury was then extracted from the solution with dithizon. The dithizon was then treated to learn how much of the mercury present in the buffered solution had reacted with it.

After we obtained the percentages, the code numbers of the drugs were given to the Lakeside Laboratories in the order of toxicity revealed by this test. Our results correlated closely with their studies of the biological toxicity of these drugs.

As an example of the results of this experiment, 100 per cent of the mercury was extracted with bichloride of mercury, which is known to be highly toxic. With Mercuhydrin, we obtained 7 per cent of the mercury content in combination with dithizon, a finding that is in agreement with our knowledge of Mercuhydrin as a drug safe for clinical use. One of these experimental drugs was Neohydrin, from which only 5 per cent of the mercury was extracted by dithizon.

It would seem logical that a test of this kind could be used in screening large numbers of organic mercurial salts, or salts of any other metal that reacts with dithizon.

Reference

1. Sollmann, T. 1948. A Manual of Pharmacology. 7th ed. Saunders. Philadelphia, Pa.

M. V. King (*Polytechnic Institute of Brooklyn, Brooklyn, N. Y.*): Since many of the more toxic mercurials do not readily dissociate free metal ion, there are two other hypotheses. One is that, with the safe drugs, the mercury is relatively unreactive and does not react with dithizon at all while, in the more toxic drugs, the mercury reacts with dithizon. The other is that they all react with dithizon, but that the dithizon complex formed with the nontoxic drugs is soluble.

James Fitzsimmons: We correlated only with toxicity. As for the complex formed by the combination of the organic mercurial and dithizon, it is true that the mercury does not split off completely from the organic radical.

M. V. King: I am suggesting that the mercury might not split off at all, but that the organic mercurial as a whole may combine with dithizon and then be extracted into the carbon tetrachloride phase, since dithizon and its complexes generally do not remain in the aqueous phase when the system is acidic.

James Fitzsimmons: We knew that mercury did not combine with dithizon as a simple mercuric ion because we got an atypical reaction, and it was necessary to take the dithizon complex in the carbon tetrachloride phase and hydrolize it with a strong solution of hydrochloric acid and then re-extract it with dithizon to get a true mercury complex that we could read by our colorimetric method.

R. E. KAUFMAN (*New York, N. Y.*): There has been a reference to differences among the mercurial diuretics and routes of administration as they affect toxic reactions.

In an article in the *Annals of Internal Medicine* in 1948, I reviewed the fatalities, recorded up to that time, following mercurial diuretic administration.[1] There had been 32 such deaths, including the one I reported, which is not a large number in view of the fact that the drugs have been used all over the world for a number of years.

The point I wanted to make, though it is generally well known now, is that every 1 of these 32 fatalities occurred after an intravenous injection, and it seemed to make no difference whether it was the first, the third, or the hundredth such injection. All the mercurials known up to 1947 had been used in 1 or more of these cases.

Reference

1. KAUFMAN, R. E. 1948. Immediate fatalities after intravenous mercurial diuretics. Ann. Internal. Med. **28:** 1040–1047.

MAXWELL GELFAND (*Post Graduate Medical School, New York University-Bellevue Medical Center, New York, N. Y.*): I should like to comment on the frequency with which the terms "toxicity" and "hypersensitivity" have been used interchangeably during these discussions. I am sure that this was not intentional, but it must be emphasized that the two words are not synonymous. A toxic effect is occasionally encountered as a result of an excessive amount employed, whereas hypersensitivity to the mercurial diuretics connotes an acquired sensitivity to a normal therapeutic dose. The latter is mediated through an antigen-antibody reaction, and the clinical picture is entirely different from the former.

JAMES E. DOHERTY (*University of Arkansas, Little Rock, Ark.*): In connection with Brown's presentation regarding reactions to mercurial diuretics, I should like to discuss oral mercurial diuretics in particular.

In the last 30 years, enormous quantities of mercurial diuretics have been used; with the increasing use of these compounds, it is not surprising that some reactions have been observed. There is a tendency to associate any of these reactions with toxicity or poisoning, an association that is probably erroneous.

At the University of Arkansas we have had the same good experience that William Leff has had in the control of chronic congestive heart failure by means of oral mercurial diuretic therapy. In 58 patients studied thoroughly and followed up for as long as 3 years, maintenance on the oral diuretic Neohydrin was possible in 44 patients without parenteral injections.

About 15 to 20 per cent of our patients experienced reactions, but most of these reactions were mild and of the gastrointestinal type.

Stomatitis and gingivitis are among the reactions most commonly encountered. Correction of oral hygiene was effective in eliminating these reactions in all of our cases, and medication was never discontinued because of them.

Nausea and vomiting proved to be a real problem in a few patients, but this difficulty was obviated, in many instances, by a reduction in dosage and a subsequent stepwise increase, as outlined previously.

The low-sodium syndrome, hypochloremic alkalosis, hypokalemia, and or overdigitalization are due to excessive diuresis; consequently, they are results of the very effective properties of the diuretic, rather than a toxic manifestation. These consequences require little explanation. Elevation of the nonprotein nitrogen may accompany any of these electrolyte disturbances.

The sensitivity reactions, which have already been discussed by Brown, constitute contraindications of further therapy because of their allergic nature. True nephrotoxicity, with appearance of blood, casts, or albumin in the urine and elevation of NPN is very rarely observed.

I was interested in a recent case report by Cáceres and Stauffer[1] indicating that subacute mercurial poisoning occurred in a patient receiving 1 tablet of Neohydrin over about a 1-year period. I am reluctant to accept this reaction as mercurial toxicity. Perhaps antecedent renal disease or undue sensitivity was responsible for this patient's picture. Present reports indicate that patients with congestive heart failure tolerate much larger doses for much longer periods of time.

FIGURE 1 represents on a composite graph 219 determinations of the nonprotein nitrogen (NPN) on 58 patients. This demonstrates the tendency of the NPN to fall when therapy is optimum, even though most of the patients were at or near dry weight at the onset of therapy. It is felt that this tendency for the NPN to fall is due to the more even and sustained diuresis produced

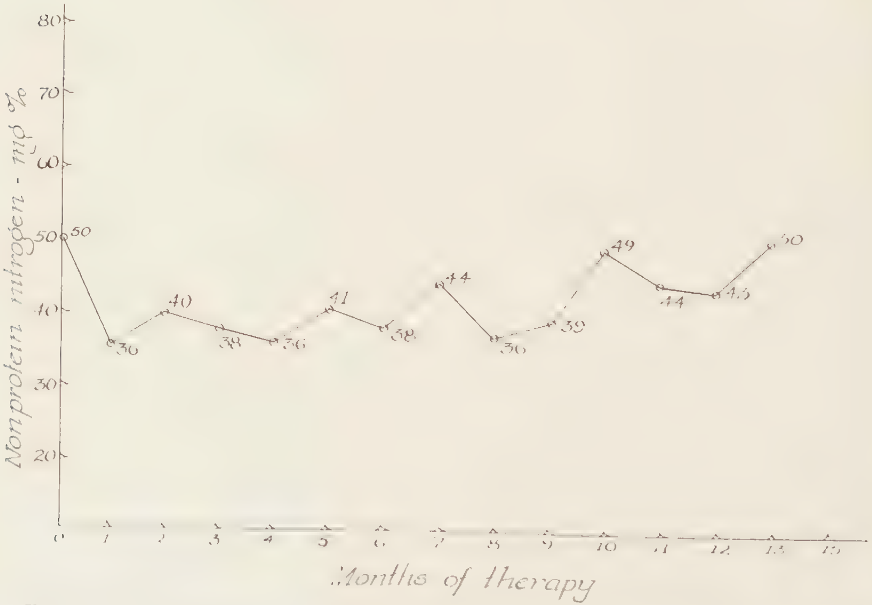


FIGURE 1. Graphic presentation of 219 determinations of the nonprotein nitrogen (NPN) of 58 patients.

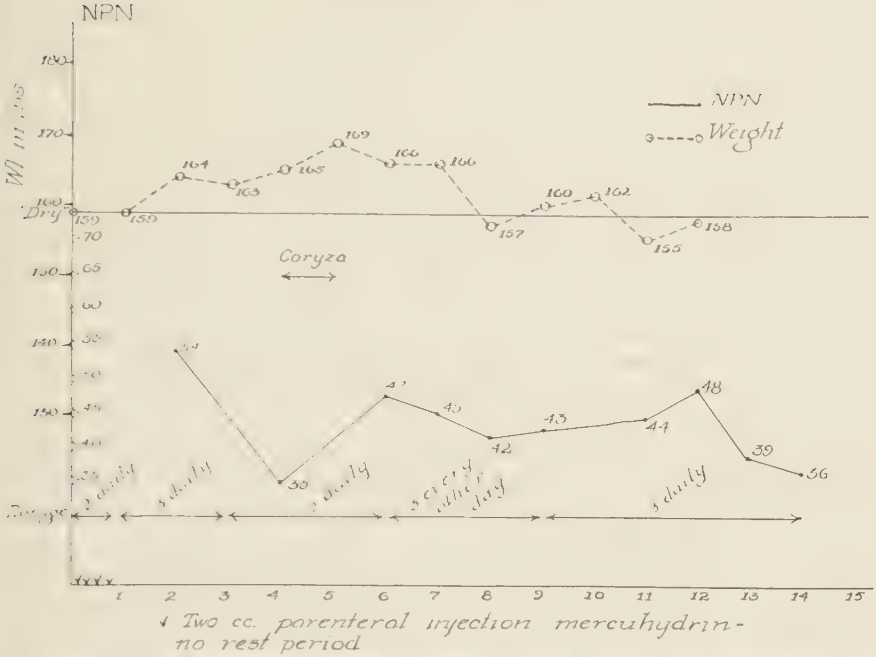


FIGURE 2. The adjustments in dosage necessary during a period when the patient had coryza, and the final readjustments resulting in a fairly stable NPN and weight.

by continuous oral diuretic therapy. The secondary rise of the NPN at 10 and 15 months illustrated here is somewhat misleading. This is due to a lesser number of determinations; actually, the data indicate that in this group of patients the figures recorded represent a fall from initial values.

The status of patients in congestive heart failure does change during periods of undue stress; as a consequence, such patients may exhibit a fluctuating NPN and changes in weight, as well as changes in severity of failure. FIGURE 2 illustrates this situation. Note the adjustments in dosage necessary during a period when the patient had coryza, and the final readjustments resulting in a fairly stable NPN and weight.

Reference

1. CÁCERES, C. A. & J. C. STAUFFER. 1955. Mercurialism: report of a case due to oral ingestion of a mercurial diuretic. New Engl. J. Med. **253**: 55–57.

W. L. HUGHES (*Brookhaven National Laboratories, Upton, N. Y.*): I have been very much impressed by the clinicians' acceptance of the new mercurial diuretics. However, I have heard no discussion of the possibility of effects on the nervous system. It is, of course, possible that the average cardiac patient may not be in a situation suitable for the observation of slight mental effects. Perhaps such effects are overlooked or do not exist, but it seems that we should have some discussion of this subject.

Leff did not mention anything in his studies about the mercury content of the brain. Some mercurial diuretics might be preferable to others because of their effects on the nervous system.

I believe it important to remain on the alert for neuropsychiatric effects in patients receiving large amounts of mercurials. Furthermore, all preparations should be of the highest stability and adequately characterized to insure the absence of even traces of mercurial impurities, which might accumulate gradually in sensitive tissues.

C. A. Handley: We have kept 50 dogs on daily mercurial injections, using 3 or 4 different kinds of diuretic compound, for as long as a year, and have found no mercury in the brain.

W. L. Hughes, Jr.: Borghgraeff and Pitts[1] have reported that dogs excrete mercurials very rapidly, at least as compared to rats. Therefore, I would question whether data on dogs are quantitatively applicable to humans.

Reference

1. Borghgraeff, R. R. M. & R. F. Pitts. 1956. The distribution of chlormerodrin (Neohydrin) in tissues of the rat and dog. J. Clin. Invest. **35:** 31–37.

Harold Shoemaker (*University of Oklahoma School of Medicine, Oklahoma City, Okla.*): Organomercurial diuretics apparently have no affinity for fatty tissues such as those of the brain. Müller[1] found no mercury in the brain of a dog sacrified 2 hours after a large intravenous injection of Salyrgan.

Aikawa and Fitz[2] have measured brain and bone concentrations of mercury following an injection of mercurial diuretic and term them "negligible."

Using mercaptomerin labeled with Hg^{203}, these investigators injected terminal patients intravenously or subcutaneously with 1 to 2 c.c. of the drug. In one patient with arteriosclerotic heart disease, who received the drug 1¼ hours before death, the concentration of mercury in the brain was found to be 0.11 µg. per gram of wet tissue, or one-ninth of a part per million. In a second patient with meningococcemia, who received the injection 10 hours prior to death, brain concentration of the mercury was found to be 0.16 µg. per gram of wet tissue, or one-sixth of a part per million.

In a third patient with rheumatic heart disease, the injection was given 144 hours before death, and no measurable concentration of mercury in the brain could be detected.

References

1. Müller, J. 1928. Tierexperimentelle Untersuchungen uber die Verteilung des Quecksilbers im Organismus und klinische Erfahrungen uber die Ausscheidung desselben nach Salyrganinjektionen. Arch. exptl. Pathol. Pharmakol. **141:** 1–18.
2. Aikawa, J. K. & R. H. Fitz. 1956. The distribution of Hg^{203} labeled mercaptomerin in human tissues. J. Clin. Invest. **35:** 775–778.

Elmer H. Funk, Jr. (*Jefferson Medical College of Philadelphia, Philadelphia, Pa.*): I should like to comment on the reference, in Brown's paper,[1] to the observation by Gold and his group[2] concerning a high incidence of irritation at the site of injection in a study in which Thiomerin was given subcutaneously. This effect was found only in use of early experimental lots, and has not been reported since then. Since the important original work by Gold and his group was done, it has been established that the present Thiomerin is a purer compound than that originally studied. In our current experience of more than 1500 subcutaneous doses of this diuretic at Jefferson and Pennsylvania Hospitals, Philadelphia, Pa., during the past several years, we have found the injections uniformly well tolerated. No significant irritation has been seen. Previous studies by Hanenson *et al.*,[3] as well as by Pote,[4] substantiate these observations. This experience is in keeping with the current monograph by the Council on Pharmacy and Chemistry.[5] It is important to clarify this so that this earlier work is correctly interpreted.

References

1. Brown, E.. A. 1956. Ann. N. Y. Acad. Sci. **65**(5): 545.
2. Gold, H., T. Greiner, S. B. Mathes, R. R. Marsh, L. J. Warshaw, W. Modell, N. T. Kwit, H. L. Otto, S. Garb, H. Bakst & M. L. Kramer. 1952. Am. J. Med. Sci. **223**: 618.
3. Hanenson, I. B., R. E. Weston, J. Grossman & L. Leiter. 1953. Med. Clin. N. Amer. : 650.
4. Pote, H. H. 1956. Personal communication.
5. A.M.A. Council on Pharmacy and Chemistry. 1956. New and Nonofficial Remedies. : 328.

M. Wachstein: In rats, a large quantity of a mercurial diuretic can produce renal damage.[1] We have administered meralluride sodium to rats in a dose equivalent to 0.01 mg. mercury per gm. body weight by intramuscular injection.[2] Incidentally, this is substantially greater on a per kilogram basis than the therapeutic dose used in humans (about 17.5 times the mercury equivalent of a 1-c.c. dose), though somewhat nearer the diuretic dose for the rat.

Within 24 hours we observed a marked necrotizing nephrosis, limited to the terminal portions of the proximal convoluted tubules. When this large dose is increased fourfold, the necrosis involves almost all of the proximal convoluted tubules through their entire course.

Obviously, it has not been possible to check experimentally the effects on the human kidney of the administration of such large doses. Occasionally, however, the pathologist is confronted with microscopic sections from kidneys of patients who for long periods of time received large doses of mercurial diuretics and who ultimately died from decompensated heart disease. In some of these sections, we have found what we consider evidence of tubular damage. In such cases, one cannot always clear mercurials of responsibility, although it must be noted that anoxia, shock, and various other factors could be responsible for renal changes such as we have observed in these instances.

References

1. Lippman, R. W. 1949. Effect of proteinuria on toxicity of mercurial diuretics in the rat. Proc. Soc. Exptl. Biol. Med. **72**: 682.
2. Wachstein, M. & E. Meisel. 1951. Protective action of certain amino acids on toxicity of mercurial diuretics in rats. Proc. Soc. Exptl. Biol. Med. **76**: 523–527.

Milton Gross (*Margaret Hague Maternity Hospital, Jersey City, N. J.*): We are heartened by the fact that oral organomercurial diuretics may be used for long periods without serious damage. We feel, however, that there is a tendency toward overemphasizing the safety of these drugs, even to the extent of advising continuous dosage with mercury for pregnancy edema. Mercurials operate as diuretics, presumably by reducing the functional capacity of active renal tubular transport mechanisms. This is accomplished by an irreversible type of enzymic inhibition resulting from mercaptide formation mainly through interaction with sulfhydryl groups of a number of cellular components.[1] Succinic dehydrogenase is especially sensitive,[2] and reduction of its activity interferes with the sequence of reactions associated with the production of energy for normal cell formation.[3] Kidney adenosinetriphosphatase is also inhibited by mercurial diuretics.[4] As a result, the specific mechanism for sodium[5] and glucose[6] reabsorption is interrupted, and tubular secretion of Diodrast, *p*-aminohippurate,[7] and phenol red[8] is depressed. Thus it would appear that the diuresis produced by mercurials is a consequence of an induced nonspecific impairment of renal tubular function.

We agree that in the cardiac patient, especially in emergency congestive situations where a rapid diuresis is mandatory, this consideration is of secondary importance. Pregnancy edema is something else, however. Although it is not yet possible to alter the underlying defect in the handling of water and electrolytes in toxemia of pregnancy, reduction in edema is desirable. This can be obtained by facilitating the excretion of abnormally retained sodium by means of a diuretic agent[9] in conjunction with dietary restriction. Still, the choice of a diuretic in pregnancy must be given special consideration, inasmuch as continuous administration for long periods is often necessary.

The kidney is hypersensitive in toxemia of pregnancy. Hypertension, proteinuria, and edema characteristic of pre-eclampsia are the same triad usually associated with renal disease. Although primary renal impairment need not underlie pre-eclampsia, when renal impairment does exist there seems to be a predisposition to acute toxemia.[10] In some instances, toxemia of pregnancy may leave residual renal damage.[10] Depression of renal plasma flow and glomerular filtration rate, and urea and uric acid clearances have been demonstrated in toxemia.[10] These alterations are due, presumably, to physiological rather than organic injury. However, unless shown to the contrary, it would appear that a diuretic agent such as mercury, which produces its effect by direct inhibition of renal cellular metabolism, is contraindicated during toxemia of pregnancy because of the possibility of augmenting the existing renal embarrassment. In addition, the lack of deleterious action of mercurials on fetal embryonal tissues must be established before these agents are administered to pregnant women.

An alternative diuretic for the treatment of pregnancy edema is the carbonic anhydrase inhibitor, acetazoleamide.[11-14] When this is given in small but effective doses, once every 24 or 48 hours, in conjunction with a limited-salt diet, control of edema and weight gain are readily maintained. Used this way, the drug has low toxicity, it is eliminated rapidly, its inhibition of carbonic anhydrase is easily reversible and evanescent, and adequate adjustment of altered acid-base equilibria is permitted. Long-term dosage evidences no alteration in renal clearances in dogs[12] or in women with toxemia of pregnancy.[13] No adverse effects on gestation in animals have been demonstrable, either maternally or on fetal development.[16] Although this agent has been found useful, the development of nonmercurial oral preparations with low toxicity but with greater diuretic potency is nevertheless to be anticipated.

References

1. Pitts, R. F. & O. W. Sartorius. 1950. Mechanism of action and therapeutic use of diuretics. Pharmacol. Revs. **2:** 161–226.
2. Wachstein, M. & F. Meisel. 1954. Influence of experimental renal damage on histochemically demonstrable succinic dehydrogenase activity in the rat. Am. J. Pathol. **30:** 147–165.
3. Schlenk, F. 1952. Succinic dehydrogenase. *In* The Enzymes, Chemistry and Mechanism of Action. J. B. Summer & K. Myrback, Eds. **2**(1): 316–328. Academic Press. New York, N. Y.
4. Goth, A., J. Holman & V. O'Dell. 1950. Effect of mercurials on kidney adenosinetriphosphatase activity. Proc. Soc. Exptl. Biol. Med. **74:** 178–180.
5. Duggan, J. J. & R. F. Pitts. 1950. Studies on diuretics. I. The site of action of mercurial diuretics. J. Clin. Invest. **29:** 365–371.
6. Weston, R. E., J. Grossman, I. S. Edelman, D. J. W. Escher, L. Leiter & L. Hellman. 1949. Renal tubular action of diuretics. II. Effects of mercurial diuretics on glucose reabsorption. Federation Proc. **8:** 164.
7. Brun, C., I. Hilden & F. Raachou. 1947. Effects of mersalyl on the renal function. Acta Pharmacol. Toxicol. **3:** 1.
8. Beyer, K. H., R. H. Painter & V. D. Wiebelhaus. 1950. Enzymatic factors in renal tubular secretion of phenol red. Am. J. Physiol. **16:** 259–267.
9. Gross, M. 1956. Toxemia of pregnancy. II. Diuretic agents in the treatment of edema of pregnancy. Classification and mode of action. Bull. Margaret Hague Maternity Hosp. **9:** 177–185.
10. Chesley, L. C. 1951. Kidney function in the normal and toxemic pregnant woman. Med. Clin. N. Am. **35:** 699–714.
11. Ashe, J. R., Jr., B. Carter, W. L. Thomas & W. R. Kerr. 1956. Diamox, a carbonic anhydrase inhibitor, as an oral diuretic in pregnancy. Obstet. Gynecol. **7:** 242–248.
12. Assali, N. S., A. Monk, R. Ullrich, J. Voskian & B. P. Singh. 1955. Effects of inhibition of renal carbonic anhydrase by Diamox in normal and toxemic pregnancies. J. Lab. Clin. Med. **46:** 733–746.
13. Gross, M., A. Gendreau, F. Liegner & R. A. Cosgrove. 1956. Toxemia of pregnancy. I. Use of acetazoleamide as an adjunct to dietary restrictions in control of edema of pregnancy. Bull. Margaret Hague Maternity Hosp. **9:** 10–15.
14. Schmieden, H. 1955. Outpatient trial of acetazoleamide in prevention of pre-eclamptic toxemia. Lancet. **1956** (ii): 1223–1225.
15. Maren, T. H., B. C. Wadsworth, E. K. Yale & L. G. Alonso. 1954. Carbonic anhydrase inhibition. III. Effects of Diamox on electrolyte metabolism. Bull. Johns Hopkins Hosp. **95:** 277–321.
16. Maren, T. H., E. Mayer & B. C. Wadsworth. 1954. Carbonic anhydrase inhibition. I. The pharmacology of Diamox, 2-acetylamino-1, 3, 4, thiadiazole, 5-sulfonamide. Bull. Johns Hopkins Hosp. **95:** 199–243.

Raymond E. Weston (*Montefiore Hospital, New York, N. Y.*): Certain available facts in the literature must be considered before we can conclude that there may be dangerous retention and/or renotoxic effects of mercurial diuretics, given in therapeutic doses, in the absence of acute renal disease. Certainly it is true, as Wachstein has pointed out, that massive doses of organic mercurials given to animals can produce gross and microscopic evidences of renal damage. However, there is no evidence that such damage can be produced by the administration of mercurial diuretics in the usual therapeutic doses to human subjects free of organic renal disease. Moreover, the excretion of organic mercurials is relatively rapid. Generally, half of the total injected therapeutic dose of mercury has appeared in the urine within 3 hours, and virtually all of it is eliminated from the body within the first 24 hours.

In addition, the rate of excretion of mercury is not diminished in such patients, even when chloriuresis and natriuresis are negligible following the administration of a mercurial.[1] Only in the presence of severe *organic* renal disease does significant mercury retention ordinarily occur following weekly or semiweekly injections of mercurial diuretics. In edematous patients with renal disease, however, the intermittent trial of parenteral mercurials, when needed, is certainly not contraindicated in the absence of an active urinary sediment.[2]

As for the reported changes in tubular function following therapeutic doses of the mercurials, these do no more than reflect the pharmacological action of these drugs on renal enzymatic processes, an action that is completely reversible. For example, although mercurials acutely depress the maximal tubular capacity for excreting para-aminohippurate ($\mathrm{Tm}_{\mathrm{PAH}}$) in man, we found that both $\mathrm{Tm}_{\mathrm{PAH}}$ and Tm_{G} were normal in a series of patients in severe congestive failure on the basis of rheumatic valvular disease, many of whom had received innumerable injections of mercurial diuretics over many years.[3]

Several discussions have alluded to the quantity of mercury found post mortem in the kidneys of cardiac patients. It must be emphasized, however, that this must necessarily be a function of the time before death the patient received a mercurial injection. Not infrequently, the terminal cardiac in severe congestive failure has been given a parenteral mercurial within a few hours before expiring. In such cases, inasmuch as there is a greater renal uptake at first, and only later a more rapid renal release of mercury,[4] concentrations of mercury found in the kidneys post mortem may be deceptively high.

Finally, it should be recognized that, as yet, there have been no reports of significant damage to either fetus or mother in the many cases of edema in pregnancy in which parenteral mercurials have been given. Once edema has been mobilized in the pregnant woman, however, as in any edematous patient, prevention of reaccumulation by strict adherence to a low-sodium intake is certainly preferable to any diuretic, oral or parenteral.

References

1. GROSSMAN, J., R. E. WESTON, R. A. LEHMAN, J. P HALPERIN, T. D. ULLMANN & L. LEITER. 1951. Urinary and fecal excretion of mercury in man following administration of mercurial diuretics. J. Clin. Invest. **30:** 1208.
2. WESTON, R. E., J. GROSSMAN, E. R. BORUN, H. A. GUERIN, H. MARK, T. D. ULLMANN, M. WOLFMAN & L. LEITER. 1953. Metabolic studies on the effects of ion exchange resins in edematous patients with cardiac and renal disease. Am. J. Med. **14:** 404-424.
3. GROSSMAN, J., R. E. WESTON, J. R. HALPERIN & L. LEITER. 1950. The nature of the renal circulatory changes in chronic congestive failure as reflected by renal tubular maximal functions. J. Clin. Invest. **29:** 1320–1326.
4. WESTON, R. E., J. GROSSMAN, R. A. LEHMAN, T. D. ULLMANN, J. P. HALPERIN & L. LEITER. 1951. Renal extraction and excretion of mercury in man following intravenously administered mercurial diuretics. J. Clin. Invest. **30:** 1221–1227.

J. W. HENDRICK (*Jacksonville, Fla.*): The discussion by Gross indicates that he is interested in the use of a carbonic anhydrase inhibitor in toxemic edema. I look forward to the continued investigation of the efficiency of Diamox in this field. In fact, I consider such study a natural consequence of the basic premise that a sodium- and water-excreting diuretic is of value in pregnancy edema. I have here the paper in which Ashe and his associates[1] report that Diamox was useful in management of this disease. Their group of patients had a fetal mortality of 3 per cent. Our group of patients on Neohydrin had a fetal mortality of just under 2 per cent. Both these figures are well within the normal 3 to 4 per cent national perinatal mortality.

As to the kidney in toxemia of pregnancy, the vasospasm of the afferent glomerular arterioles contributes to the proteinuria, rather than to any basic organic pathology, and the blood urea nitrogen is normal before and after therapy. Normal renal function after true toxemia of pregnancy is a fact accepted by most workers, and we also have found this to be the case. If chronic hypertensive or renal disease existed prior to toxemia, then, of course, the previous dysfunction will still be present. Naturally, careful renal study in toxemia and afterwards is indicated. Again, as noted in my earlier remarks, this fearful attitude toward the kidney in toxemia was prevalent in 1950 when we began our study; clinical and laboratory observations since then have failed to reveal any reason to deny the patient such an important adjunct to treatment as the diuresis of sodium and water. Note also that toxemia of pregnancy is not usually a long-term disease and that, even when a maintenance therapy of 2 to 4 Neohydrin tablets daily is indicated, the time of therapy is the last month of pregnancy.

As to the mechanism of action of mercurials, this has been fully discussed by previous members of this symposium. We find no reason based on enzymatic inhibition of sodium resorption to deny their use to our patients.

Finally, in our fairly prolonged experience with mercurials in toxemia of pregnancy, we have noted no harmful effects on either mother or child. In 2 cases in which we obtained amniotic fluid prior to delivery in patients who were receiving mercurial diuretics, we could not demonstrate the presence of any mercury therein.

Moreover, in our use of mercurial diuretics in the toxemias of pregnancy since 1951, as well as in the 200 cases reported here and in the additional cases we have treated subsequently, we have observed no increase in fetal mortality or morbidity. I do not know of any such observations in the literature.

Each physician must use that method of therapy which he finds most effective and, although I look forward with interest to reports on the use of Diamox, my associates and I, and evidently the majority of the contributors to this monograph, find that the most potent and effective diuretics are mercurials.

Reference

1. Ashe, J. R., Jr., B. Carter, W. C. Thomas & W. R. Kerr. 1956. Diamox, a carbonic anhydrase inhibitor, as an oral diuretic in pregnancy. J. Obstet. Gynecol. 7: 242–248.

George Griffith (*University of Southern California School of Medicine, Los Angeles, Calif.*): Both our clinical impression and histological findings (figures 1 and 2) support the statement that patients free from significant renal disease may be maintained for months or years on moderate or massive doses of organomercurials without injury to kidney function, provided neither oliguria nor hyponatremia is present. Administration of mercurials to patients with

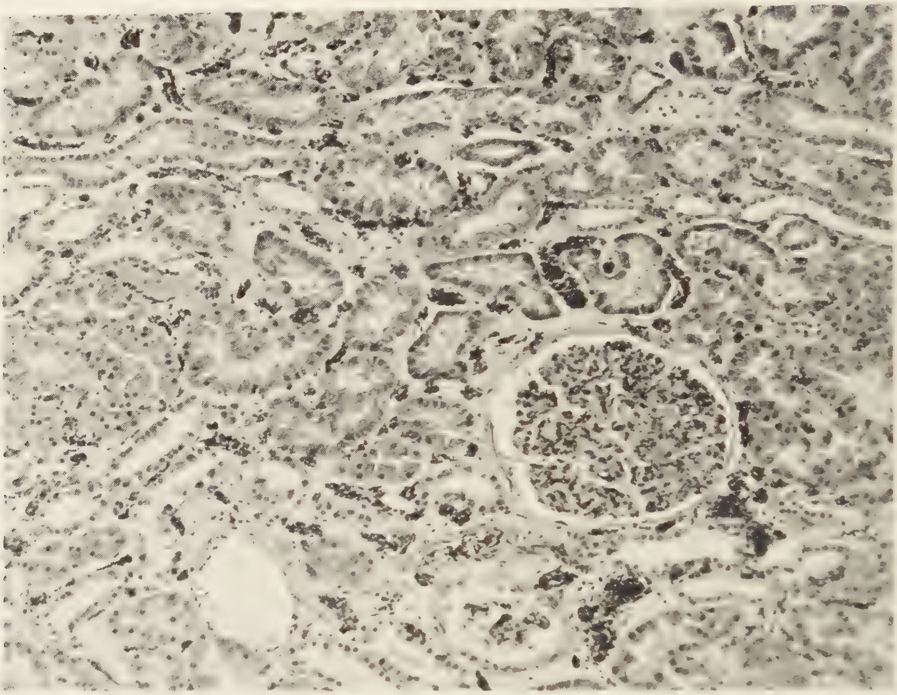


FIGURE 1. Case No. 1117. Kidney ×150. (Hg content 50.1 mg. per 100 gm. dried kidney tissue.) Kidney showing no evidence of mercurial toxicity. Intense congestion of glomerular and intertubular capillaries. Slight parenchymatous change involving the proximal convoluted tubules.

oliguria or hyponatremia may cause temporary damage to the renal tubules, but complete regeneration of the tubules occurs once mercurials are withdrawn.

RALPH M. SUSSMAN (*Beth Israel Hospital, New York, N. Y.*): I think that it has been abundantly demonstrated that mercurial diuretics are not nephrotoxic to humans at therapeutic dose ranges over long periods of time. Mercuhydrin has been employed extensively for more than 10 years, and one finds only rare reports of renal toxicity following its ingestion.

In discussing the long-term use of the mercurial diuretics, over periods as long as 10 years, let us not forget that reactions that have occasionally been attributed to mercurial diuretics can be caused by the diseases for which we use these drugs, by the condition of the patients to whom we give them, and even by much simpler substances to which the patients may have been exposed for a protracted period. An example of the latter is the milk-alkali syndrome that results from the excessive use of milk and sodium bicarbonate, which might lead to irreversible renal impairment.

In some cases of diabetic intercapillary glomerulosclerosis associated with congestive failure and moderate elevation of the N.P.N. to about 50 or 60 mg. per 100 ml., the administration of organomercurials may be followed by signs

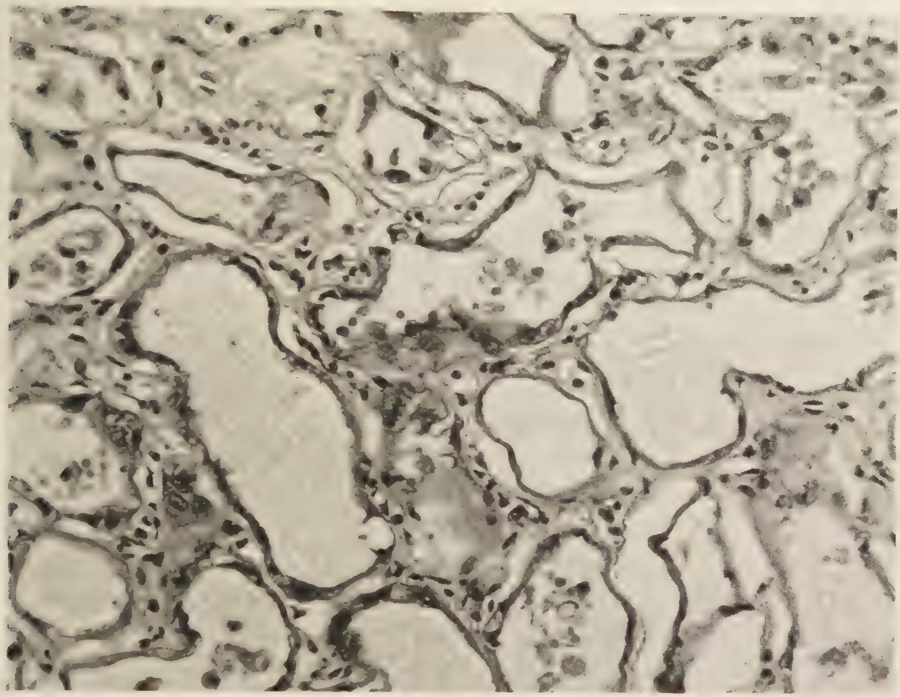


Figure 2. Case No. 78. Kidney ×275. (Hg content 18 mg. per 100 gm. of dried kidney tissue) Regeneration areas of kidney. Proximal convoluted tubules lined by flattened dark-staining cells. Note the mitotic figure.

of intoxication, such as stomatitis and gingivitis, with grayish membranes in the tonsillar region, accompanied by diarrhea. In these instances, the renal failure preceded the use of the mercurial diuretics and was responsible for the toxic reactions. As cardiac failure increased, a prerenal factor was added to the renal disturbance.

Recently, 4 cases of the nephrotic syndrome were reported by Munck and Nissen,[1] who ascribed the renal disease to the use of mercurial diuretics. Careful review of this paper does not establish the organomercurials as the cause of the nephrotic syndrome. As patients live longer, they will suffer from a variety of degenerative diseases that may sometimes include the kidneys. Cases in which the nephrotic syndrome occurs in the course of vascular deterioration, with or without associated diabetes mellitus, have been observed before mercurial diuretics were employed for their management. To blame these drugs for such renal disturbances seems unwarranted in the light of clinical experience.

Since the use of mercurial diuretics for pre-eclampsia would be only a temporary measure, one can find little objection to their use in this condition.

Such small amounts of mercurials as are found in the kidney after long-term therapy do not detract from the usefulness of the mercurial diuretics, which have added comfortable years to the lives of many patients. As these patients grow older, we shall inevitably see more advanced pathological conditions. It is my belief that most clinicians feel quite safe in using the modern mercurial diuretics so far as the kidneys are concerned.

It should be emphasized that these remarks do not apply to inorganic mercurial preparations or to instances of idiosyncratic reactions to mercurial diuretics.

Reference

1. Munck, O. & N. I. Nissen. 1956. Development of nephrotic syndrome during treatment with mercurial diuretics. Acta Med. Scand. **153**(iv): 307–313.

John Moyer: In our 2-year study using chlormerodrin (Neohydrin) for the treatment of heart failure,[1] we found that, at the effective dosage level of 6 to 8 tablets per day (60 to 80 mg. Hg), serious toxic manifestations such as cardiac and renal toxicity did not appear over a 2-year period as far as could be determined by urinalysis, phenolsulfonphthalein (P.S.P.) and urea clearance tests, and by electrocardiography. We can conclude that the organomercurials have not altered the functional capacity of the kidney in these patients. Although pathological evidence of renal changes due to mercurial diuretics has been reported, it is extremely difficult to determine whether these histological alterations have resulted from the organomercurial or from passive congestive and tissue anoxia associated with terminal and intractable heart failure.

In our studies, there was no evidence that blood dyscrasias had developed. Gastrointestinal manifestations occurred in about one fourth of the patients. In 3 of 28 patients, diarrhea was serious enough to require discontinuation of the diuretic. Five additional patients experienced intermittent diarrhea which was tolerable, and the diuretics were continued. Gastrointestinal irritation was minimized by administering Neohydrin in divided doses with meals. It was our opinion that the diarrhea was more serious when the patients began with a large dose than when the initial dose was small and was subsequently increased over a period of 4 to 8 weeks. Although gastrointestinal disturbances had a high nuisance value and somewhat limited the therapeutic usefulness of chlormerodrin, there were no permanent untoward effects, and these effects were usually not of sufficient severity to cause discontinuation of the drug. As soon as the diuretic was discontinued in those patients showing disturbances in gastrointestinal function this abnormality returned to the control state.

About one third of the patients develop weakness and fatigue, associated with diuresis, during therapy with Neohydrin alone and in combination with Diamox. The incidence of side effects during therapy with Diamox is low. These side effects consist primarily of weakness, lethargy, and paresthesias.

I think that the differences in patient populations are worth noting. In clinic patients at a city or county hospital, who usually are in severe heart failure before they seek medical treatment, the incidence of side reactions is considerably lower than in private patients, who are usually seen before the heart failure is severe. The incidence of side effects seems to be slightly higher in normal individuals and in those patients with only mild congestive heart failure. For example, when those of us who are relatively normal took chlormerodrin, the incidence of diarrhea was quite high. I need take only one chlormerodrin tablet to suffer a violent attack of diarrhea. By contrast, the patient who has heart failure is usually troubled with constipation, probably due to passive congestion of the bowel. The cathartic effect of chlormerodrin in such a patient is frequently beneficial.

I think that these differences in the types of patient being treated may often explain the differences in the incidence of toxicity observed in various clinics and, consequently, they may also explain differences in reports coming from different investigators.

Reference

1. Moyer, J. H., C. A. Handley & I. Wilford. 1952. Results over a 2-year period on 3 experimental diuretics administered orally to patients with cardiac failure. Am. Heart J. **44:** 608–614.

Ethan Allan Brown (*Allergy Section, Boston Dispensary Unit, New England Medical Center, Boston, Mass.*): One of the important problems in the dissemination of knowledge concerning present-day treatment methods is that of communicating these concepts and techniques of treatment, free of past inaccurately conventional and, often, nonpertinent points of view. This is particularly true in the case of the mercurial compounds.

Consider, as a contrasting example, the case of penicillin. Its introduction was accompanied by the conviction that it was free of toxicity and caused no untoward reactions. Time, widespread use, and further research have yielded increasing evidences of reactions to this antibiotic agent, many of them severe and some of them fatal. Despite this fact, the past history of penicillin makes it difficult today to achieve a balance between its efficacy and the calculated risk involved in its use.

Earlier experience with metallic mercury, mercury vapor, the inorganic salts of mercury, and some of the older organic compounds gave mercury a bad pharmacological reputation that has persisted in the face of rather impressive research indicating that the newer organomercurial agents are chemically and pharmacologically different from all previously used mercury compounds. We should not loosely refer to these new compounds as "mercury" because they do not dissociate into free mercury, and they behave quite differently from mercury in clinical studies. These drugs, moreover, differ from one another, and they should be so discussed; and, if compared, comparison should be made at the levels of dosage at which each is therapeutically effective.

Such evidence notwithstanding, it has been stated that "in rats, a large quantity of mercurial diuretic can produce renal damage," and it is suggested, therefore, that this finding should serve as a warning against the administration of such diuretics. An examination of the experimental data cited to support this view shows that the doses given were, on a per kilogram basis, from 17.5 to 70 times as large as those given to humans.

Have we a right to extrapolate from mice to men, or to draw any clinical conclusion whatsoever from experiments involving doses of such magnitude?

As the author of this comment himself points out, it has not been possible, for obvious reasons, to check experimentally the effects on the human kidney of such large doses. Of course, water itself, in quantities so many times the normal requirements, will also produce adverse reactions.

Perhaps, however, it should be pointed out that, even in rats, a dosage of over 8 times that given to humans, on a per kilogram basis, has been found by Cafruny, Farah, and Di Stefano[1] to produce an effect on sulfhydryl concentrations that is reversible in from 6 to 24 hours, depending on the part of the kidney involved.

Finally, many other factors could have caused the renal damage seen in those few cases of humans in whom it has been observed. Just as it is obviously impossible to exclude mercury as a causative factor, it is impossible scientifically to implicate or to exclude the other possible causes.

This and other evidence here presented directly challenges the assertion that the action of mercurial diuretics is an "irreversible enzymic inhibition." Actually, this statement, carried to its logical conclusion, would lead to the inference that one or a few doses of a mercurial diuretic would cause a prolonged, if not a lifetime, diuretic effect, which is patently absurd.

The source given for the assertion of irreversibility[2] does not, on careful inspection, support the critic's point. On the contrary, Pitts, the senior author of the work in question, in a more recent paper speaks of "the logical assumption that organic mercurial compounds combined *reversibly* with certain cellular enzymes. . . ."[3]

The introduction into this discussion of such concepts as "tendency toward overemphasizing the safety of these drugs" and "advocating continuous dosage with mercury" hardly adds to our factual information. Any "overemphasis" is by definition wrong. Certainly no one is "advocating" the administration of *mercury* but, rather, reporting on the action of specific organomercurial complexes.

Almost all of the specific points connected with edemas of pregnancy have been settled, but certainly this can be a serious "emergency situation," and the most effective treatment is obviously called for, especially in view of the fact that the disorder is involved with a definite time limit, as distinguished from the cardiac, who must be given the drug, we hope, for a matter of years.

As for the suggestion that studies must be done on fetal embryonal tissues, is this not true of any medicinal agent given to pregnant women? Certainly the reported observations on amniotic fluid, demonstrating an absence of mercury in any form, are worthy of note, especially since they *are* observations on human subjects.

As for the use of acetazolamide in the edemas of pregnancy, omitting the question of comparative potency, we have in the literature ample reports of reactions following the administration of this drug. Again, long-term use of organomercurials in large series of patients with toxemic edemas is reported to have produced no untoward clinical reactions. All the other evidence supports this present-day position.

Progress in pharmacology and careful research both would seem to have established the fact that, with proper patient selection and management, the organomercurial compounds can be used effectively with a margin of safety the same as or greater than with other potent drugs in common use.

These considerations are important because, unless there is good evidence to the contrary, we wish to use the most effective agent available. Our decision, however, must accord with current facts, and not be based on older prejudices. We want to use the organomercurial in a fully effective dose. It is significantly apparent from the papers presented here that some clinicians have swung from the earlier practice of administering doses that are too large to the use of minimally effective doses. In all fairness to any drug in the treatment of any disorder, it is obvious that either extreme is not the best practice of medicine.

The suggestion has been made that we should concentrate our efforts on the search for drugs at once more potent and less toxic. While this is always a laudable goal, as Ray[4] has pointed out, it is a fact that our diuretic drugs are already sufficiently potent. At this time, we must be primarily concerned with the optimal management of our present patients on the presently available drugs that have proved to be effective in doses permitting a wide margin of safety.

References

1. Cafruny, E. J., A. Farah & H. S. Di Stefano. 1955. Effects of the mercurial diuretic mersalyl on protein-bound sulfhydryl groups in the cytoplasm of rat kidney cells. J. Pharmacol. Exptl. Therap. **115:** 390–401.
2. Pitts, Robert F. & Otto W. Sartorius. 1950. Mechanism of action and therapeutic use of diuretics. J. Pharmacol. Exptl. Therap. **98:** 161–226.
3. Borghgraeff, R. R. M. & R. F. Pitts. 1956. The distribution of chlormerodrin (Neohydrin) in tissues of the rat and dog. J. Clin. Invest. **35:** 31–37.
4. Ray, C. T. 1956. Diuretic therapy. Cardiovascular Conference. 105th Ann. Meet. Am. Med. Assoc., Chicago, Ill.

Part III. Clinical Medicine

THE MODE AND MECHANISM OF MERCURIAL DIURESIS IN NORMAL SUBJECTS AND EDEMATOUS CARDIAC PATIENTS*

By Raymond E. Weston
Medical Division, Montefiore Hospital, New York, N. Y.

Our group at Montefiore Hospital has been interested for some time in the renal site and mechanism of mercurial diuresis in man. Our interest has been twofold. First, as clinicians, we felt that better understanding of the mode of action of mercurial diuretics would lead to improved applications of these most valuable therapeutic agents in the management of edematous patients, particularly those in so-called intractable congestive failure. Second, as clinical investigators, we felt that if the precise renal tubular locus of action of the mercurial diuretics could be established, these drugs could be valuable tools for analyzing the dichotomy of function between the proximal and distal renal tubular segments as regards the excretion of strong electrolyte.

The evolution of current concepts regarding these and other important aspects of the pharmacology and clinical application of mercurial diuretics will be reviewed by considering some of our studies of the past decade. Our earliest work dealt with one phase of the problem; namely, an analysis of the factors contributing to the unresponsiveness to mercurial diuretics, which develops in many patients in severe congestive failure.[1] For a long time, the ultimate failure of these patients to give a diuretic response to organic mercurials was attributed by some to the development of renal tubular resistance to the action of mercury. It was well known, however, that many patients in less severe failure continue to give satisfactory response to these drugs for years. Moreover, renal tubular functions other than electrolyte reabsorption are affected by mercurials to the usual degree in the mercurial-resistant cardiac patient. This is illustrated (TABLE 1) by the 60-per cent decrease in the renal tubular capacity for excreting para-aminohippurate ($\mathrm{Tm}_{\mathrm{PAH}}$), 2 hours following a therapeutic parenteral dose of a mercurial that produced no water diuresis or chloriuresis.

Others have attributed mercurial resistance chiefly to chloride depletion,[2, 3] because pretreatment with chloride salts potentiates diuresis in patients previously unresponsive to mercurials. However, the diuretic response to mercurials is often unrelated to serum electrolyte levels in many patients.[3, 4]

On the other hand, since diuresis represents the difference between the quantities of electrolyte and water delivered to, and that reabsorbed by the renal tubules, it is evident that response to mercurials may be diminished or even

---

* Part of the work reported in this paper was supported by grants from the National Heart Institute, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Md; the Martha Hall Foundation, Montefiore Hospital, New York, N. Y.; Eli Lilly & Co., Indianapolis, Ind.; Wyeth Inc., Philadelphia, Pa.; Campbell Pharmaceuticals, Inc., New York, N. Y.; G. D. Searle & Co., Chicago, Ill.; Lederle Laboratories, Pearl River, N. Y.; the New York Heart Association, New York, N. Y.; the American Heart Association, New York, N. Y.; and Sandoz Pharmaceuticals, Hanover, N. J. It represents the collective efforts of the author and of Jacob Grossman and Louis Leiter, assisted by Research Fellows and other colleagues.

TABLE 1

EFFECT OF THIOMERIN ON Tm_{PAH} AND CHLORIDE EXCRETION OF MERCURIAL-RESISTANT PATIENT IN CONGESTIVE FAILURE*

Period	GFR	Plasma PAH	Tm_{PAH}	Chloride excretion	Urine volume
	ml./min.	mg./min.	mg./min.	mEq./min.	ml./min.
Control	47.1	0.600	79.6	.002	3.05
Mercury	32.0	0.923	32.0	.026	3.80

* Reproduced by permission from the *Journal of Clinical Investigation* [1]

completely abolished by any factor that either increases tubular reabsorption or otherwise decreases the load of filtered electrolyte presented for excretion. We felt that mercurial resistance in cardiac patients in congestive failure could represent another manifestation of the severe impairment in renal salt and water excretion resulting from the changes in cardiovascular-renal hemodynamics, hormonal balance, and other mechanisms promoting salt retention. It is apparent that one of these factors, the decrease in glomerular filtration, reduces the quantity of filtered sodium and chloride reaching the renal tubules. Observations from a number of laboratories have established that, whenever filtration is reduced without alteration in the tubular function, the consequent glomerulotubular imbalance leads to virtually complete tubular reabsorption of sodium. Early in congestive failure, inhibition of tubular reabsorption by administration of a mercurial will lead to diuresis, despite a moderate reduction in filtration rate. However, the continued fall of glomerular filtration rate in advanced congestive failure finally decreases the filtered electrolyte load so severely that negligible diuresis occurs even after mercurial inhibition of tubular activity.

Preliminary studies soon established that most patients who no longer respond to mercurial diuretics have very low glomerular filtration rates. Therefore, experiments were designed to test the hypothesis that reduced filtration rate was contributing to the poor diuretic response. It is well known that the xanthine compound, aminophylline, when intravenously administered, produces significant increase in glomerular filtration rate in normal subjects and in patients in congestive failure. As TABLE 2 demonstrates, the intravenous injection of 0.72 gm. of aminophylline alone in a patient in chronic congestive failure with a moderately reduced glomerular filtration rate generally produces a significant increase in GFR and in sodium load, but only a moderate increase in excretion of electrolyte. When the same dose of aminophylline is given 2 hours after the injection of an organic mercurial, however, so that the filtration rate is increased at the time of maximal mercurial depression of renal tubular reabsorption, the patient's diuresis is considerably augmented.

TABLE 3 illustrates the effect of aminophylline, intravenously administered 2 hours after a mercurial diuretic, on the renal hemodynamics and electrolyte excretion of mercurial-resistant patients. In each case, the resulting increase in filtration rate is associated with a significant augmentation of mercurial

TABLE 2

COMPARISON OF EFFECT OF AMINOPHYLLINE AND MERCUZANTHIN PLUS AMINOPHYLLINE IN CHRONIC CONGESTIVE FAILURE*

Patient	Period	RFP	GFR	Serum Na	Serum Cl	Na filtration	Na excretion	Cl filtration	Cl excretion	Urine volume
		ml./min.	ml./min.	mEq./l.	mEq./l.	mEq./min.	mEq./min.	mEq./min.	mEq./min.	ml./min.
E. G.	Control	—	65.0	139	—	8.99	0.004	—	—	1.60
	Aminoph.	—	90.0	142	—	12.8	0.020	—	—	4.37
H. G.	Control	247	71.2	132	91.8	9.49	0.009	7.34	0.031	1.44
	Mercury	231	69.5	132	91.5	9.27	0.125	7.13	0.203	2.19
	Aminoph.	347	90.4	132	89.1	12.0	0.738	9.00	0.939	7.45

* Reproduced by permission from the *Journal of Clinical Investigation.*[1]

diuresis. However, a review of this table reveals that, in addition to decreased filtration rates, many of these patients also have significantly reduced serum sodium and chloride concentrations, which not only would further decrease the load of filtered electrolyte delivered to the tubules, but might also tend to promote sodium retention or otherwise antagonize the mercurial effects in other ways.

Therefore, we next studied the effect on mercurial diuresis of increasing both renal hemodynamic function and serum electrolyte concentrations by infusing

TABLE 3

EFFECT OF THE INCREASED GFR FOLLOWING AMINOPHYLLINE INJECTION ON MERCURIAL DIURESIS IN MERCURIAL RESISTANT PATIENTS*

Patient	Period	RPF	GFR	Serum Na	Serum Cl	Na filtration	Na excretion	Cl filtration	Cl excretion	Urine volume
		ml./min.	ml./min.	mEq./l.	mEq./l.	mEq./min.	mEq./min.	mEq./min.	mEq./min.	ml./min
C. R.	Control	115	41.1	122	84.3	5.01	0.002	3.82	0.004	2.78
	Mercury	99	36.1	120	84.6	4.32	0.005	3.37	0.021	1.86
	Aminoph.	139	46.5	119	84.6	5.51	0.165	4.34	0.285	4.69
E. S.	Control	197	55.8	114	92.4	6.36	0.002	5.70	0.006	1.94
	Mercury	164	46.4	112	88.7	5.20	0.026	4.59	0.050	2.23
	Aminoph.	228	59.6	114	85.1	6.78	0.389	5.64	0.614	8.04
B. G.	Control	175	60.9	116	82.4	7.06	0.002	5.05	0.001	2.23
	Mercury	148	56.0	120	81.5	6.75	0.003	4.43	0.002	1.94
	Aminoph.	212	66.3	120	78.8	7.96	0.020	5.23	0.062	3.47
J. B.	Control	211	60.7	135	88.8	8.29	0.149	6.07	0.150	8.98
	Mercury	188	53.2	137	90.1	7.49	0.199	5.38	0.216	5.44
	Aminoph.	269	75.8	137	89.9	10.5	0.896	7.65	0.807	14.1
A. B.	Control	80	45.7	117	89.5	5.38	0.001	4.57	0.003	0.80
	Mercury†	81	44.1	115	85.7	5.05	0.014	4.20	0.045	2.14
	Aminoph.	115	61.0	115	85.4	7.00	0.227	5.76	0.371	7.11

* Reproduced by permission from the *Journal of Clinical Investigation.*[1]

† In this case the patient received 2 ml. Thiomerin. The other patients received 2 ml. Mercuzanthin.

TABLE 4

EFFECT OF CONCENTRATED SODIUM INFUSIONS ON THE DIURETIC RESPONSE OF CARDIAC PATIENTS TO MERCUZANTHIN*

Patient	Period	Time	RPF	GFR	Serum Na	Serum Cl	Na filtration	Na excretion	Cl filtration	Cl excretion	Urine volume
		min.	ml./min.	ml./min.	mEq./l.	mEq./l.	mEq./min.	mEq./min.	mEq./min.	mEq./min.	ml./min.
E. S.	Control	0–53	194	55	123	89	6.74	0.002	5.32	0.004	1.97
	5% NaCl†	124–140	192	62	139	107	8.60	0.006	7.32	0.018	1.25
	Mercuzanthin‡	194–204	194	82	136	107	11.1	1.13	9.74	1.44	12.1
		204–214	190	84	135	104	11.4	1.22	9.71	1.43	12.5
		214–227	187	75	135	103	10.2	0.998	8.55	1.29	11.4
		227–237	195	69	135	103	9.33	0.930	7.85	1.23	10.7
		237–246	188	67	135	102	9.07	0.854	7.56	1.14	10.3
		246–259	176	65	135	101	8.74	0.725	7.30	0.946	8.88
A. R.	Control	0–48	195	62	126	95	7.89	0.059	6.55	0.141	4.80
	Mercuzanthin§	138–150	191	54	125	95	7.28	0.445	5.70	0.710	8.89
	Conc. Na Inf.**	178–188	267	59	137	102	8.08	1.19	6.76	1.53	14.1
		188–198	264	62	138	103	8.50	1.41	7.05	1.72	15.5
		198–208	266	62	140	106	8.73	1.60	7.34	1.93	16.5

* Reproduced by permission from the *Journal of Clinical Investigation.*[1]

** 5% NaCl (550 ml.) + molar Na lactate (80 cc.) infused i.v. at 5 ml./min. from minutes 161 to 208.

† 5% NaCl infused i.v. at 4.5 ml. min. from minutes 53 to 173.

‡ Mercuzanthin 2 ml. i.v. at minutes 145–146.

§ Mercuzanthin 2 ml. i.v. at minutes 55–57.

5-per cent sodium chloride solution, containing sufficient molar sodium lactate to maintain the normal serum sodium chloride ratio, in mercurial-resistant patients, including several from the earlier series. TABLE 4 presents data on one of these patients (E.S.), who, 6 weeks after the previous studies, again exhibited reduced serum electrolyte concentrations, filtered electrolyte loads, and excretion rates. Over a 2-hour period, during which 450 mEq. of a 4.5-per cent sodium chloride solution were administered intravenously, there was no significant change in sodium and chloride excretion, despite the increase in glomerular filtration rate and serum electrolyte concentrations. However, when a mercurial diuretic was given after the concentrated salt infusion was completed, the augmentation of the filtered electrolyte load was associated with profuse diuresis. Following the peak diuresis, the gradual fall in glomerular filtration rate was associated with a decrease of sodium chloride and water excretion, despite the maintenance of the serum sodium level.

As indicated by the data on this patient, the early period of a concentrated salt infusion generally produces only slight increase in electrolyte excretion of cardiacs without renal disease.[5] However, administration of such infusions for 2 hours prior to giving the mercurial might have influenced the diuretic response by affecting some base-conserving mechanisms, thereby independently decreasing tubular reabsorption of electrolyte. Therefore, to demonstrate that the increased response to mercurials under these circumstances was due,

TABLE 5

IMMEDIATE EFFECT OF CONCENTRATED SODIUM INFUSION ON MERCURIAL DIURESIS IN CHRONIC CONGESTIVE FAILURE*

Patient	Period	RPF ml./min.	GFR ml./min.	Serum Na mEq./l.	Serum Cl mEq./l.	Na filtration mEq./min.	Na excretion mEq./min.	Cl filtration mEq./min.	Cl excretion mEq./min.	Urine volume ml. min.
B. G.	Control	62	21.8	114	82	2.48	0.001	1.79	0.000	.09
	Mercuzanthin	57	22.9	111	82	2.56	0.003	1.88	0.000	1.06
	5% NaCl†	81	24.8	112	84	2.78	0.007	2.09	0.000	1.20
		97	27.3	115	86	3.13	0.040	2.60	0.192	2.56
		111	29.5	119	88	3.50	0.115	2.88	0.307	3.64
		111	29.5	122	92	3.62	0.204	3.02	0.410	4.57
		110	29.6	125	94	3.70	0.263	3.10	0.467	4.88
	Stop Inf.	113	30.3	126	95	3.83	0.309	3.20	0.528	5.18
		99	25.8	126	93	3.26	0.208	2.67	0.384	3.97
		100	24.5	125	91	3.06	0.121	2.47	0.292	3.18
G. R.	Control	142	56.1	129	100	7.30	0.005	6.31	0.016	5.10
	Thiomerin	181	69.1	129	100	8.98	0.020	7.74	0.098	10.3
		166	67.2	129	101	8.76	0.021	7.53	0.087	8.81
		186	67.9	130	101	8.89	0.428	7.61	0.595	12.9
		175	65.7	130	101	8.65	0.823	7.46	1.08	14.5
		167	65.4	130	101	8.62	0.817	7.42	1.08	13.0
		154	61.4	130	101	8.10	0.723	7.00	0.995	11.0
	5% NaCl‡	170	61.3	134	103	8.27	0.805	7.07	1.10	11.1
		206	66.3	138	105	9.24	1.11	7.85	1.37	11.8
		219	71.3	139	105	9.99	1.25	8.42	1.50	13.4

* Reproduced by permission from the *Journal of Clinical Investigation.*[1]
† 5% NaCl i.v. at 3 ml./min.
‡ 5% NaCl i.v. at 6 ml./min.

in part, to the augmentation in filtered electrolyte load, the filtered load of electrolytes was acutely increased in other patients (TABLE 5) by injecting the concentrated sodium solutions 2 hours after giving the mercurial, when maximal tubular depression of tubular activity presumably is present. Under these circumstances, in one of the patients (G.R.) the increased filtered load, resulting from giving a concentrated salt infusion when diuresis had begun to wane, led to a marked augmentation in excretion of electrolyte, which finally reached 150 per cent of the maximum levels achieved with the mercurial alone.

The other data in TABLE 5 are on a female patient (B.G.) who previously had exhibited a slight potentiation of diuresis after the injection of aminophylline alone. In the 3 weeks since the previous study, her clinical condition had deteriorated rapidly, and her filtration rate and renal plasma flow had decreased more than 50 per cent. Once again, there was no increase in the urinary excretion of electrolyte in the first 2 hours after injection of a mercurial. However, when concentrated salt solution was then infused at a rate of 3 ml. min., sodium, chloride, and water excretion increased progressively as filtration rate, renal plasma flow, and serum electrolyte concentrations rose.

TABLE 6

AUGMENTATION OF MERCURIAL DIURESIS BY ADMINISTRATION OF CONCENTRATED SODIUM INFUSION AND AMINOPHYLLINE TO MERCURIAL RESISTANT PATIENT M. M.*

Period	Time	RPF	GFR	Serum Na	Serum Cl	Na filtration	Na excretion	Cl filtration	Cl excretion	Urine volume
	min.	ml./min.	ml./min.	mEq./l.	mEq./l.	mEq./min.	mEq./min.	mEq./min.	mEq./min.	ml./min.
Control	0–70	54.4	21.3	107	72.4	2.36	0.004	1.70	0.015	1.66
Mercuzanthin†	149–167	57.6	20.8	103	72.9	2.13	0.014	1.66	0.042	2.62
Conc. Na‡	167–180	86.4	29.1	113	79.4	3.26	0.232	2.54	0.276	6.62
	180–192	83.0	26.3	117	81.5	3.06	0.219	2.36	0.294	5.59
	192–205	83.5	26.9	117	81.9	3.02	0.215	2.38	0.298	5.57
	205–216	87.5	27.3	116	80.7	3.13	0.231	2.42	0.318	5.36
Aminophylline§	216–225	132.0	36.1	114	79.5	4.10	0.806	3.21	0.817	12.6
	225–233	94.0	34.5	113	78.9	3.86	0.639	2.99	0.642	10.7
	233–242	88.0	31.2	112	78.2	3.47	0.441	2.68	0.506	8.94

* Reproduced by permission from the *Journal of Clinical Investigation.*[1]

† Mercuzanthin 2 ml. at minutes = 70.

‡ 5% NaCl (430 ml.) + molar Na lactate (120 ml.) inf. i.v. at 8 ml./min. from minutes = 167–177, and at 4 ml./min. from minutes = 177–242.

§ 0.50 gm. i.v. from minutes = 211–216.

Urinary electrolyte excretion was greatest when the filtered sodium and chloride loads were maximal, but fell sharply as the filtration rate declined after the concentrated salt infusion was discontinued, despite the persistent increase in renal plasma flow and serum electrolyte levels. However, because of this patient's far-advanced congestive failure, as reflected by the marked impairment in renal hemodynamics, the electrolyte excretion rate never approached that observed during a good mercurial response.

It is of interest to note that, with the concentrated salt infusion, better mercurial diuresis occurred at a filtered sodium load of only 3.8 mEq./min. than in the previous mercurial-aminophylline study when the filtered sodium load was 8.3 mEq./min. This suggests, as indicated above, that the hypertonic salt solution not only increases the filtered load, but also affects other mechanisms influencing mercurial diuresis.

TABLE 6 illustrates the effects of more rapidly infusing a concentrated salt solution 96 minutes after giving a mercurial to a patient who had the most severely impaired renal hemodynamics and the lowest serum electrolyte levels encountered in a large series of cardiacs without renal disease. The infusion was at a rate of 8 ml./min. for 10 min., and then at a rate of 4 ml./min. to the end of the study. The increases in urinary excretion of electrolyte and water, which occurred promptly, persisted as the improved renal hemodynamics, serum electrolyte levels, and serum load were maintained. When aminophylline was given intravenously 40 minutes later, the immediate increase in renal hemodynamics and filtered electrolyte load was associated with a striking additional rise in electrolyte and water excretion, although the serum sodium and chloride concentrations were only 114 and 80 mEq./l., respectively.

These data appeared to establish the fact that one factor contributing to

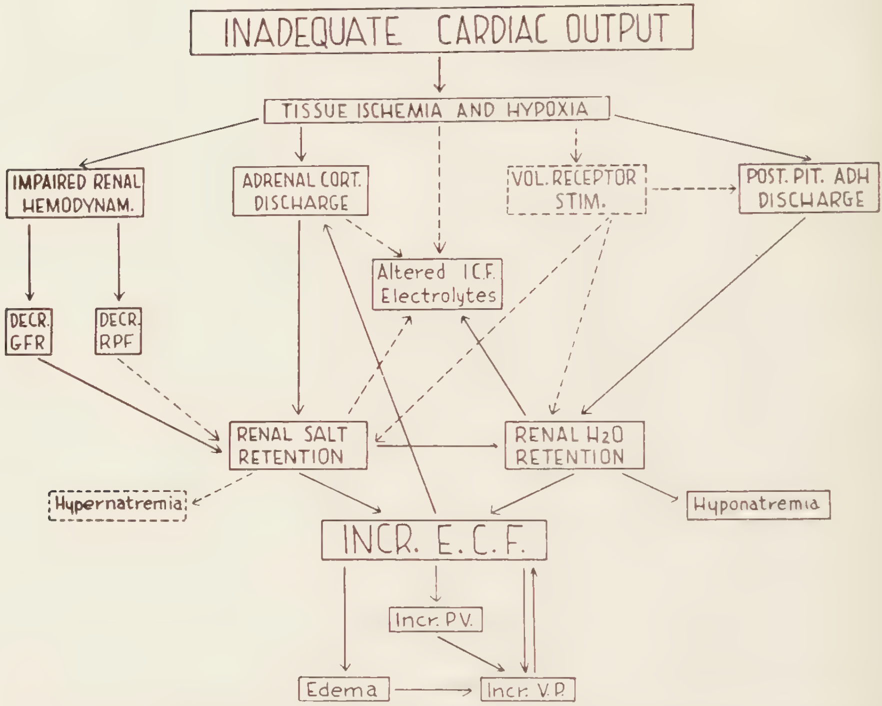


FIGURE 1. Mechanisms promoting salt and water retention when cardiac output becomes inadequate for the body's metabolic needs. (Reproduced by permission from *Medical Clinics of North America.*[11])

the resistance of certain cardiac patients to the diuretic effects of organic mercurials is the decreased load of electrolyte delivered to the tubules. Although these observations have since been repeatedly confirmed,[6] it should be emphasized that mercurial diuresis will be reduced by any factor that induces renal salt conservation.

In congestive failure, as indicated in FIGURE 1, a number of mechanisms are activated that promote salt and water retention whenever the cardiac output becomes inadequate for the body's metabolic needs. Among these are impaired renal hemodynamics; increased adrenal cortical discharge; alterations in intracellular and extracellular fluid and electrolyte distribution; sustained or increased posterior pituitary antidiuretic hormone release; and, finally, certain mechanisms that function to maintain the circulation by preserving normal body fluid volume distribution.

The effect on mercurial diuresis of adrenal cortical steroids, which increase tubular salt reabsorption, is illustrated by the data in TABLE 7. This patient (G.R.), when given a mercurial after receiving 4 injections of 5 mg. of desoxycorticosterone acetate at 6-hour intervals in the previous 24 hours, exhibited a lesser diuretic response than she had previously (TABLE 5), although her body weight, clinical condition, and serum electrolyte levels were the same. Not

TABLE 7

EFFECT OF PRETREATMENT WITH DESOXYCORTICOSTERONE ACETATE* ON MERCURIAL DIURESIS IN PATIENT G. R.†

Period	RPF	GFR	Serum Na	Serum Cl	Na filtration	Na excretion	Cl filtration	Cl excretion	Urine volume
	ml./min.	ml./min.	mEq./l.	mEq./l.	mEq./min.	mEq./min.	mEq./min.	mEq./min.	ml./min.
Control	175	59.4	130	93.6	7.84	0.007	6.21	0.011	5.98
Thiomerin	164	60.5	129	93.4	7.84	0.011	6.29	0.009	7.23
	161	60.6	129	94.1	7.87	0.009	6.36	0.016	7.29
	161	59.4	130	94.9	7.73	0.011	6.28	0.023	6.63
	150	55.4	130	94.7	7.20	0.015	5.84	0.035	5.94
	147	52.1	130	94.6	6.78	0.031	5.49	0.061	5.79
	148	53.6	130	93.9	7.00	0.071	5.60	0.125	6.65
	156	54.6	130	92.7	7.11	0.143	5.64	0.229	8.25
	150	53.1	129	91.9	6.91	0.171	5.44	0.268	8.76
	154	54.2	129	91.0	7.01	0.273	5.51	0.402	10.6

* 4 Doses of DCA (5 mg./6 hours).
† Reproduced by permission from the *Journal of Clinical Investigation*.[1]

only was her response to the mercurial considerably diminished, but it was much slower in onset, and it gradually increased over several hours. Others[7] have also reported that pretreatment with corticotropin or desoxycorticosterone acetate (DCA) will inhibit mercurial diuresis. It should be emphasized that this inhibition depends upon the duration of such pretreatment, as well as on other factors. Thus, it was recently reported that no inhibition of mercurial diuresis occurred in dogs to whom DCA was administered for a number of days.[8] By the time the mercurial was given to these animals, however, compensation for the effects of steroid on the tubules had already been achieved, and the animals were no longer retaining electrolyte. If a mercurial is given before this phase of compensation has been reached, however, decreased diuretic response results when corticotropin or adrenal steroids are administered.[1, 7]

The activation of salt-conserving mechanisms in congestive failure may explain certain other aspects of mercurial diuresis. For example, it is well established that, during mercurial diuresis in patients exhibiting marked sodium retention, potassium excretion increases, and there is generally more excretion of chloride than of sodium. The best explanation for these 2 phenomena is that the kidney can actively conserve sodium without chloride by distal tubular transport of hydrogen, ammonia, and potassium. Whenever the body responds to a stimulus leading to sodium retention, these ion-exchange mechanisms are stimulated, perhaps by the increased release of adrenal cortical steroids. As a result, sodium that has escaped reabsorption because of mercurial inhibition of some more proximal tubular function may be actively exchanged for other cations by these distal tubular processes which are not affected by therapeutic doses of mercurials.[1, 3, 9]

The data in TABLE 8 demonstrate the increased potassium excretion and decreased excretion of sodium relative to chloride occurring in a patient during mercurial diuresis, after daily administration of 20 mg. of DCA for 4 days. It should be noted that the more prolonged administration of this steroid only

TABLE 8

THE EFFECT OF PRETREATMENT WITH DESOXYCORTICOSTERONE ACETATE (DCA)* ON MERCURIAL DIURESIS IN PATIENT G. R.†

	Period	Time	Urine vol.	Urinary electrolyte excr.			Serum electrolytes		
				Na	Cl	K	Na	Cl	K
		min.	ml./min.	mEq./min.	mEq./min.	mEq./min	mEq./l.	mEq./l.	mEq./l.
Before DCA	Control	100–0	1.70	0.005	0.004	0.030	138	102	5.40
	Thiomerin‡	0–30	1.90	0.012	0.021	0.024			
		30–60	3.17	0.187	0.200	0.036			
		60–90	5.83	0.432	0.478	0.057			
		90–152	2.93	0.320	0.363	0.051			
		152–182	2.38	0.266	0.301	0.047			
		182–240	2.82	0.233	0.307	0.046	138	101	4.87
After DCA	Control	91–0	3.10	0.004	0.014	0.047	139	106	5.63
	Thiomerin‡	0–30	3.90	0.040	0.048	0.049			
		30–60	4.14	0.217	0.281	0.060			
		60–90	5.23	0.334	0.449	0.092			
		90–150	3.22	0.218	0.332	0.106			
		150–180	2.10	0.176	0.292	0.112			
		180–240	1.52	0.099	0.196	0.092	139	105	4.50

* 20 mg. of DCA/day for 4 days.
† Reproduced by permission from the *Journal of Clinical Investigation.*[1]
‡ 2 ml. of Thiomerin.

qualitatively altered, but did not abolish, the diuretic response to the mercurial, as mentioned above.

Thus, distal tubular sodium-conserving mechanisms may be responsible for the greater chloriuresis than natriuresis, which some investigators have cited as evidence that mercurials primarily inhibit chloride reabsorption. However, during mercurial diuresis in normal individuals who are not on low-sodium diets or steroid therapy, equivalent amounts of sodium and chloride are lost in the urine, and potassium excretion does not increase. Therefore, it may well be that mercurials act primarily to inhibit reabsorption of sodium and associated anions, as others have suggested.[10]

It must be emphasized that both the infusions of concentrated salt and the administration of aminophylline probably do not potentiate mercurial diuresis solely by increasing the filtered electrolyte load. For example, in cardiac patients, aminophylline invariably produces an increase in renal plasma flow that not only may lead to the increased excretion of electrolyte but may also reflect a less persistent but significant increase in cardiac output, with resulting decrease in venous pressure. The consequent cardiovascular improvement may lead to further augmentation of sodium excretion by interrupting some of the other mechanisms that promote salt retention in cardiac failure, particularly after the depression of renal tubular reabsorption by a mercurial. Similarly, the administration of the concentrated salt infusions may also have influenced body-fluid distribution or endocrine mechanisms affecting renal electrolyte excretion.

Although unresponsiveness to mercurial diuretics may be a result of a number of mechanisms, careful evaluation of the clinical status of an individual patient may often uncover a single critical causal factor, the correction of which permits better therapy. For example, the commonest cause of poor diuretic response is myocardial failure due to inadequate digitalization. Under these circumstances, the marked disproportion between cardiac output and body metabolic needs so intensifies the various factors described above that there is virtually no response to mercurials, despite adjuvant therapy with ammonium chloride and aminophylline. Unsuspected infections or active rheumatic fever may have the same effect. In such cases, it is common clinical experience to find that increasing the dose of digitalis or treating a severe respiratory infection in a desperately ill patient may lead to spontaneous diuresis or to improved response to mercurials.

When increasing doses of digitalis to the point of toxicity or therapeutic response, we generally give the patient oral potassium salt supplements because of the causal relationship between the depletion of myocardial potassium and the development of arrhythmias that do not necessarily reflect an overdosage of digitalis.[11] Once adequate digitalization has been achieved, 6 to 9 gm. of ammonium chloride are given daily in divided doses for 3 days. On the fourth day, 2 ml. of parenteral mercurial are given; 2 hours later 0.25 to 0.5 gm. of aminophylline are cautiously injected intravenously, over a period of 5 to 10 min. to avoid any reactions, especially in older individuals. After receiving the mercurial, the patient is absolutely restricted to bed, because activity decreases the excretion of salt and water. Following this procedure, excellent diuresis frequently can be achieved in patients who hitherto were completely unresponsive to mercurials.

It should be noted that infusions of hypertonic salt solutions were given experimentally to establish the roles of filtered electrolyte load and serum electrolyte concentrations in mercurial responsiveness. However, this procedure is not only therapeutically impracticable, but is generally harmful except in the presence of acute *depletion hyponatremia* associated with vascular collapse and, perhaps, further impairment of renal function.[1] Ordinarily, the amount of sodium given to improve the diuretic response is so great that the net effect is to produce more edema. In the usual cardiac dilution hyponatremia, hypertonic solutions, which only intensify congestive failure, are definitely contraindicated.[12]

Simultaneously with these studies on mercurial resistance, we began investigating the site and mode of diuretic action of mercurials in man.[10] At the time, it was known that, in animals, when toxic doses of mercurial are given, the anatomic changes are manifested primarily as microscopic lesions in cells of the proximal renal tubules. Moreover, that mercurials did interfere significantly with proximal tubular function in man was established by reports that certain proximal tubular functions such as the secretion of iodopyracet (Diodrast) and para-aminohippurate, and the reabsorption of uric acid, calcium, and glucose are significantly—though reversibly—depressed by therapeutic doses of mercurials.

It is generally accepted, however, that the aniso-osmotic reabsorption of

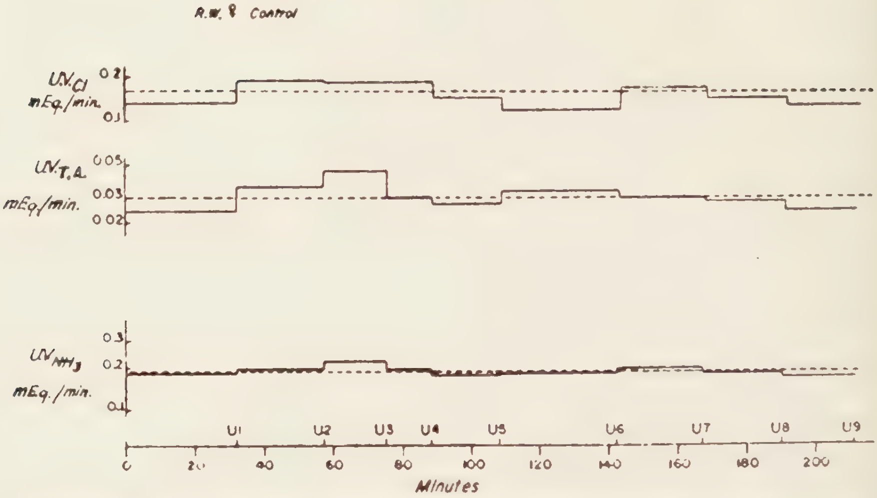


FIGURE 2. Control experiment demonstrating the constancy of urinary excretion of ammonia, titratable acidity, and chloride in an acidotic subject in the absence of a mercurial diuretic. (Reproduced by permission from the *Journal of Clinical Investigation*.[9])

water and electrolyte, which requires energy expenditure, occurs in the distal tubule. Although it seemed strange that a heavy metal such as mercury did not influence the distal tubular enzyme systems involved in this process, no direct evidence was available to indicate that ordinary therapeutic doses of organic mercurials produce any anatomic or functional changes in the distal tubular segments. We therefore undertook a study of the effect of organic mercurials on 2 renal functions, the production of urinary ammonia and of titratable acidity, which are generally considered to be localized in the distal tubule.

To provide a stimulus to these tubular functions, the subjects were rendered acidotic by pretreatment with 9 to 12 gm. of ammonium chloride daily for several days. The resulting augmented urinary excretion of ammonia, titratable acidity, and chloride remains fairly constant over a 4-hour period when no mercurial is administered (FIGURE 2). However, when the acidotic subject is given a mercurial diuretic (FIGURE 3), ammonia production is unaffected, but the urinary titratable acid increases significantly. At first, the fact that mercury, an enzyme inhibitor, should increase an active tubular process was puzzling. However, urinary titratable acid production in acidosis is a direct function of the amount of buffer available to the distal tubular segments.[13] Therefore, the increased titratable acidity during mercurial diuresis could result from mercurial inhibition of tubular reabsorption in a more proximal site, making additional phosphate and other buffers available to the more distal tubular segments that acidify the urine. Subsequent studies revealed that, during periods of enhanced titratable acidity following a mercurial, there were the anticipated increases in urinary phosphate excretion (FIGURE 3).

Generally, the load of phosphate or other buffer delivered to the distal tubules

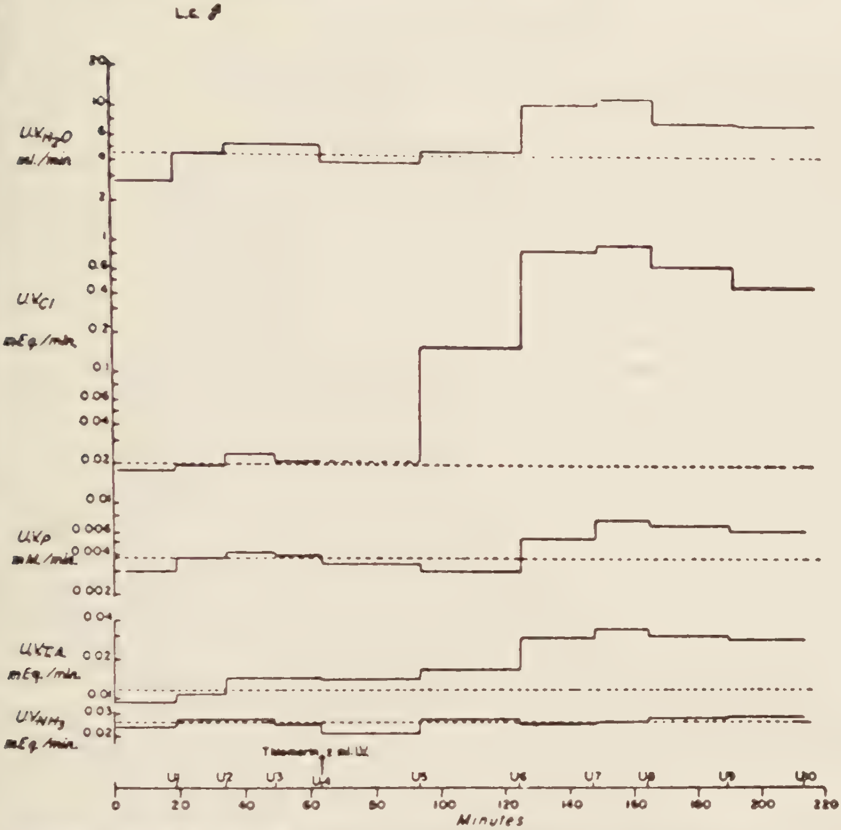


FIGURE 3. Parallel increase in urinary excretions of phosphate and titratable acid during mercurial diuresis. Reproduced by permission from the *Journal of Clinical Investigation*.[9])

is so small that, before the mercurial is given, urinary titratable acidity is only one tenth of that observed when sodium phosphate solutions are infused in acidotic men.[13] Following administration of the mercurial, the increased distal buffer load resulted in a titratable acid excretion that was only 10 to 30 per cent of that observed during infusions of phosphate. These considerations suggested that the lack of inhibition of titratable acid production that was observed during mercurial diuresis was due, perhaps, to the fact that the experimental design failed to provide a buffer load sufficient to strain this distal tubular function prior to mercurial administration. Under such conditions, partial mercurial depression of titratable acid production might be masked by the greater increase resulting from the augmented load of buffer that escapes proximal reabsorption and is thereby delivered to the distal tubules. Therefore, in other acidotic subjects, by giving continuous infusions of isotonic sodium phosphate at a *p*H of 7.3, titratable acid production was maintained at much higher levels before and following the administration of a mercurial

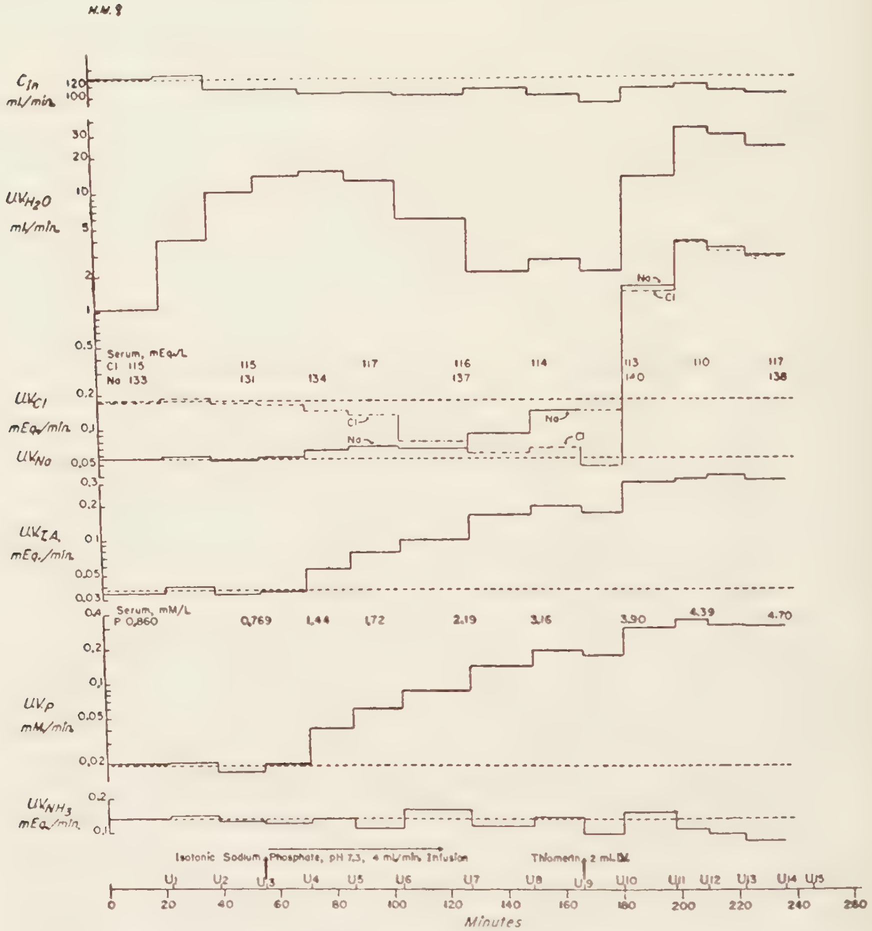


FIGURE 4. Parallel increase in the urinary excretion of phosphate and titratable acid during a phosphate infusion prior to and following the administration of Thiomerin. (Reproduced by permission from the *Journal of Clinical Investigation*.[9])

diuretic. During such infusions, as FIGURE 4 indicates, the greater distal load of phosphate is reflected in higher excretion of both urinary phosphate and titratable acid. As in the earlier experiments, however, with the onset of mercurial diuresis, titratable acid production increased as urinary phosphate excretion was further augmented. These data more firmly established the fact that mercurial diuresis enhances rather than depresses the production of titratable acid.

Because the excretion of ammonia also involves an exchange for sodium in the distal tubular fluid, the increased load of sodium delivered to the distal tubule of the acidotic subject, following mercurial inhibition of reabsorption more proximally, might enhance the ion-exchange process, thereby masking

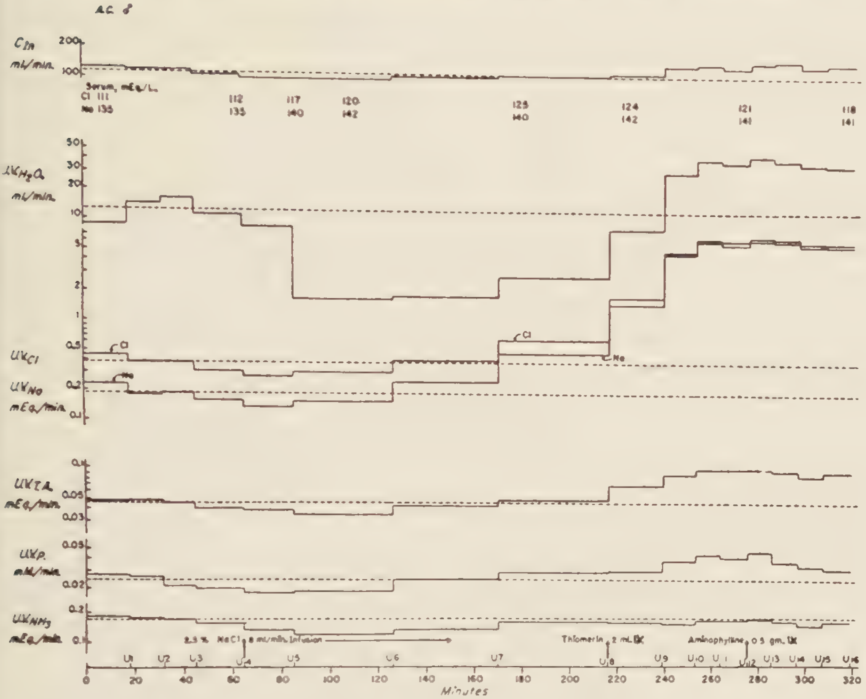


FIGURE 5. The urinary excretion of ammonia, titratable acidity, and electrolytes during a concentrated sodium chloride infusion prior to and following the administration of a mercurial diuretic. Reproduced by permission from the *Journal of Clinical Investigation.*[9])

mercurial depression of this function. Therefore, titratable acid and ammonia production were measured before and during the rapid infusion of a $2\frac{1}{2}$-per cent sodium chloride solution in an acidotic subject for approximately 90 min. prior to the administration of the mercurial diuretic. During the concentrated salt infusion (FIGURE 5), despite the increase in glomerular filtration rate and sodium excretion, the urinary excretion of ammonia and titratable acid remained at about control levels. However, the rise in serum sodium level led to increased production of antidiuretic hormone and a fall in urine volume.

When the infusion was continued and a mercurial diuretic was administered, there was profuse water, sodium, and chloride diuresis and a doubling of titratable acid excretion without change in ammonia production. At the peak of diuresis, the urine volume was 42 ml. min., or 33 per cent of the filtration rate, and approximately 34 per cent and 39 per cent of the filtered sodium and chloride, respectively, were excreted in the urine. Administration of aminophylline at this time led to further increases in the filtration rate and in the urinary excretion of water, sodium, and chloride.

This study not only confirmed the impression that mercurials do not depress ammonia production in acidotic subjects, but it also provided other interesting data. First, the maximal rates of electrolyte and water excretion, even when corrected for the increases resulting from the rapid sodium infusion, greatly exceeded those attributable to the inhibition of distal tubular reabsorption alone. Second, the changes in the urinary electrolyte concentration during diuresis suggested a provocative approach to the analysis of the renal tubular site of action of the mercurials.

During the administration of the hypertonic salt solution prior to giving the mercurial, the increased production of posterior pituitary antidiuretic hormone leads to decreased urine flow and a rise in urinary electrolyte concentration. When no mercurial is given, continuation of such an infusion generally leads to an increase in urine flow to about 6 ml./min., with a sodium concentration of 170 to 190 mEq. l.[10] If, as in animals receiving large doses of Pitressin,[13] mercurials do not affect distal tubular facultative water reabsorption but do inhibit distal tubular electrolyte reabsorption, mercurial diuresis should result in even higher urinary electrolyte concentration. Actually, as the volume of urine increases following the mercurial injection, urinary electrolyte concentration falls very sharply toward isotonicity. Mathematical analysis of the data suggests that the decrease in urinary electrolyte concentration during diuresis probably represents dilution of the hypertonic urine elaborated in the distal tubule as a result of mercurial inhibition of iso-osmotic reabsorption in a more proximal tubular site. The additional filtrate, like that escaping proximal reabsorption during an osmotic diuresis, is relatively unaffected by the distal tubules, which are already reabsorbing water at a nearly maximal rate and are not influenced by the mercurial.

When our studies on the renal site and mechanisms of mercurial action were initiated, iso-osmotic proximal reabsorption was generally considered to be passive, and, consequently, to involve minimal expenditure of energy. Therefore, in seeking the locus of mercurial action in the renal tubule, attention was focused largely on the distal segment of the tubule, where reabsorption of water and electrolyte was presumed to involve an aniso-osmotic and, consequently, active process. Since that time, however, abundant evidence has established the fact that active proximal tubular reabsorption of sodium and associated anions occurs.[15] Consequently, it is possible that mercurial diuresis may represent an inhibition of this active but iso-osmotic reabsorption in the proximal tubules. Although Duggan and Pitts[6] suggested that mercurials may act primarily by depressing distal reabsorption of electrolyte and water, they felt their data could support the view that mercurials act largely on the proximal tubules, if it is assumed that there are 2 proximal mechanisms for reabsorbing sodium, only one of which is mercury-sensitive. Mudge, Foulks, and Gilman[16] also concluded that mercurials inhibit proximal tubular reabsorption in dogs subjected to forced osmotic diuresis. The failure of mercurials to affect the several distal tubular functions studied, while inhibiting other presumably proximal functions, and the anatomic localization of the renal lesions following toxic doses of mercurials in animals also suggest that much of the diuretic effect of mercurials is exerted proximally. Although more recent histochemical studies[17] also support this view, certain other observations[18] make it difficult to state absolutely that these drugs do not affect the distal segments as well.

The increasing urinary electrolyte excretion during an infusion of concen-

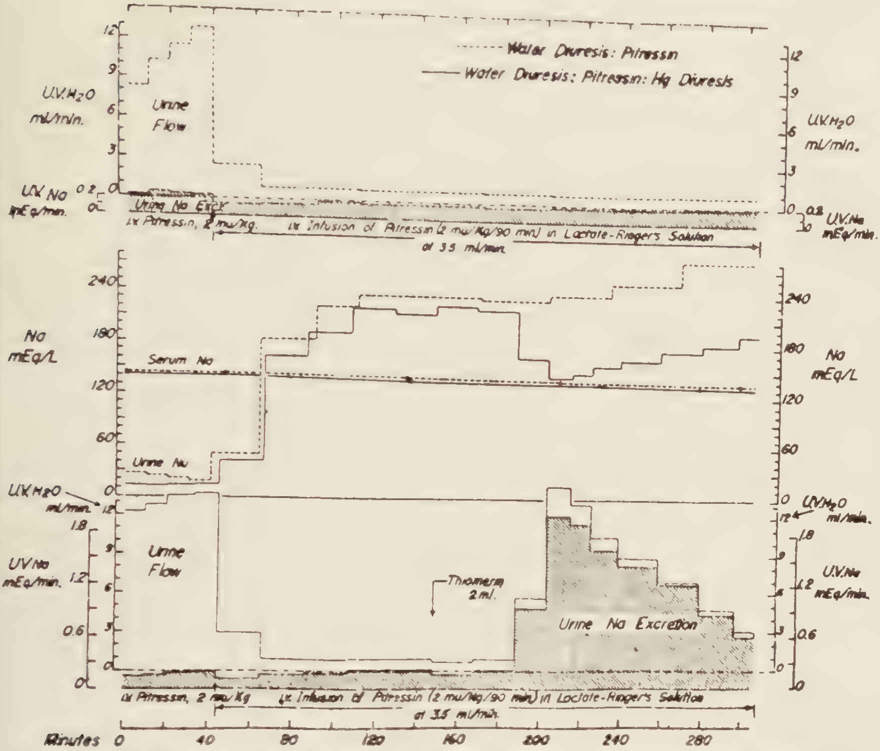


FIGURE 6. Comparison of a control (Pitressin alone) and experimental (Pitressin plus mercurial) procedure in the same subject (M. S.). (Reproduced by permission from the *Journal of Clinical Investigation*.[9])

trated salt solution complicates the analysis of the data of the previous study. Accordingly, in a series of normal subjects, constant but virtually maximal distal water reabsorption was maintained by administration of physiological doses of aqueous Pitressin following an initial intravenous priming dose.[19] FIGURE 6 presents the comparison of a typical control study with a later study in which a mercurial diuretic was given after equilibration had occurred on the same doses of Pitressin. A sharp drop in the urine volume after the injection of Pitressin was accompanied by a marked rise in urinary sodium concentration, which was maintained until the mercurial diuretic was given. Then, with the onset of diuresis, as urinary volume and sodium excretion increased, urinary sodium concentration fell asymptotically toward that of the plasma. Subsequently, as the diuresis began to wane and the urinary volume and sodium excretion fell, urinary sodium concentration increased toward the previous maximal levels.

Preliminary inspection of these data would appear to support our previous hypothesis that a small volume of concentrated urine elaborated during the infusion of Pitressin is diluted by an increasingly large volume of isotonic fluid rejected by the tubule during mercurial diuresis. Under such circumstances, the urinary concentration must always exceed isotonicity no matter how great the diuresis may be. However, added insight concerning the mechanism of mercurial diuresis is achieved if the volume and electrolyte concentration of the additional fluid rejected by the renal tubules as a result of mercurial action are calculated. This tubular rejectate, as we defined it, represents the numerical difference between the urinary excretion of water and electrolyte during the control periods and during mercurial diuresis.

The concentration of each ion in the rejectate may be calculated by dividing the electrolyte content of the tubular rejectate by the volume thereof. Such calculations revealed that at the onset of diuresis, when the rejectate volume was small, the tubular rejectate sodium and total solute concentrations were hypertonic, but they fell rapidly and asymptotically toward isotonicity as the volume of the urine and, therefore, of the rejectate, continued to increase.

At first, this finding seemed anomalous. However, it soon became apparent that the best explanation was that during mercurial diuresis, in patients receiving continuous Pitressin infusions, a small additional volume of water is reabsorbed from an isotonic tubular rejectate, probably at a point distal to the site of mercurial action. Early in the course of diuresis, the reabsorption of this additional fluid without electrolyte results in a very significant increase in the calculated rejectate electrolyte and total solute concentrations. As diuresis increases, however, the distal tubular capacity to reabsorb water at a given dose of Pitressin is exceeded, and this small increment of water reabsorbed becomes of progressively lesser importance. Subsequently, the increasing volume of isotonic rejectate continues to dilute the concentration of both the hypertonic urine and the initially highly concentrated tubular rejectate. The additional distal tubular water reabsorption required to produce the observed rejectate solute concentrations during diuresis is small relative to the normal distal reabsorption of 15 to 20 ml. min. occurring under these conditions.

This concept is illustrated by the hypothetical diuresis curve in FIGURE 7, which presents the relationship between tubular rejectate sodium concentration and volume, based on the assumption that a constant increment of 0.3 ml./min. of water without solute is absorbed, despite an increasing diuresis that results from mercurial inhibition of an iso-osmotic reabsorptive process. The fact that the actual data for all the subjects fit the theoretical curve supports this hypothesis and suggests that the capacity of the distal tubule to reabsorb water is limited by two factors: the maximal concentration gradient between the tubular lumen and the plasma, and the maximal rate at which the tubules can reabsorb water per se.[11] Although, normally, the osmotic ceiling is the principal determinant of distal water reabsorption, under the special circumstances of mercurial or osmotic diuresis the maximal reabsorptive capacity to reabsorb water may be exceeded before the maximal concentration gradient is reached.

A further extension of this analysis explains another interesting aspect of the data. When the urine sodium or total solute concentrations or excretion rates during the course of diuresis are plotted against the corresponding urinary or rejectate volumes it can be seen that, as diuresis wanes, the curve never

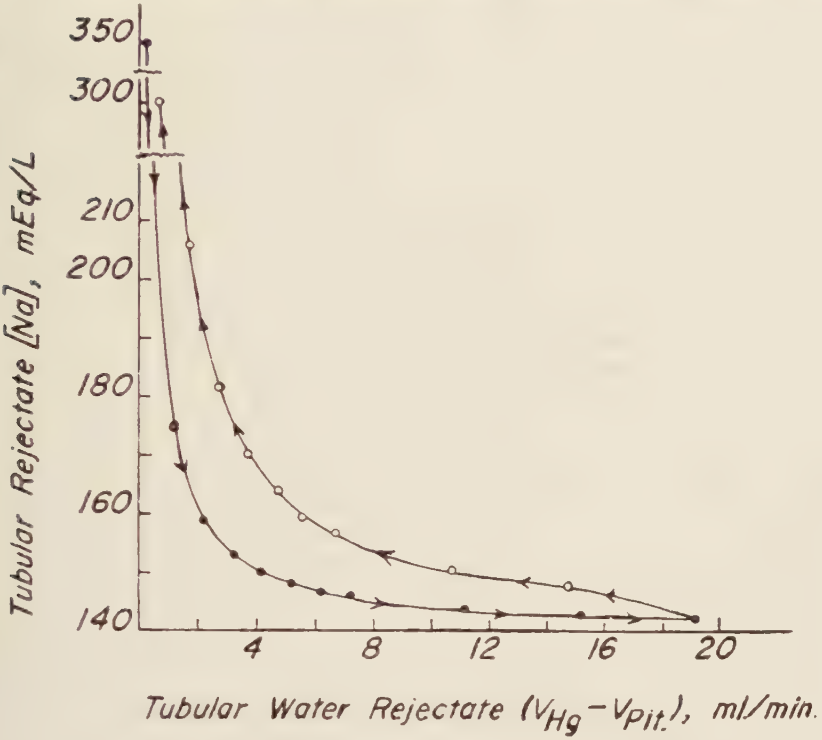


FIGURE 7. The relationship between tubular rejectate sodium concentration and tubular rejectate volume. This hypothetical diuresis curve is based upon the following assumptions: at the onset (Pitressin alone), the urine flow is 1.0 ml./min., and urinary sodium concentration is 288 mEq./l. During the increasing diuresis a constant increment of 0.3 ml./min. of water without solute is absorbed; following maximal flow, an additional 0.5 ml./min. of water is reabsorbed. It is apparent that, at smaller urine flows, additional reabsorption of a given amount of water without solute will produce a considerably greater increase in tubular rejectate sodium concentration than at higher flows. Reproduced by permission from the *Journal of Clinical Investigation.*[19])

retraces the path followed during the phase of increasing diuresis. If mercurial diuresis were a relatively simple process in which urine flow followed osmotic load, rising to a maximum and subsiding as the pharmacological effects of the mercury were dissipated, the plot of concentration versus volume should rise and fall symmetrically along the same path. Actually, at any given volume during the phase of waning diuresis, in these studies the urine is invariably more concentrated than during increasing diuresis. This finding would suggest that, following maximum diuresis, the kidney may be reabsorbing more water per unit of sodium or of total solute than it did previously (FIGURE 7).

This possibility is supported by the calculated free water clearances (FIGURE 8), which demonstrate that after the initial slight increase in water reabsorption during the onset of mercurial diuresis there is no further effect on free water clearance until diuresis subsides. At this point the negative free water clearance for any given free water flow is higher than during the period of in-

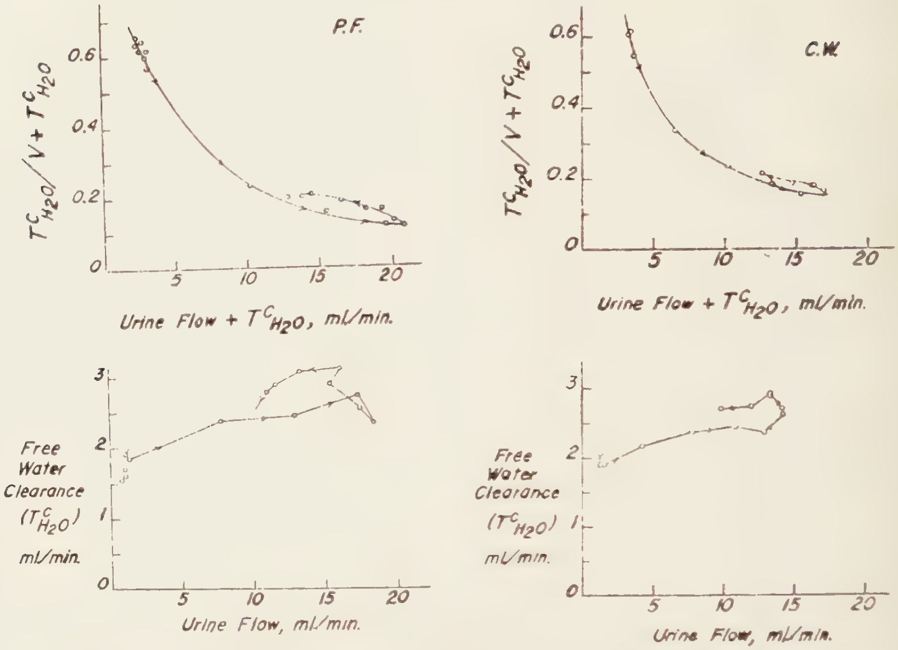


FIGURE 8. Changes in negative free water clearance during the course of diuresis.

In the lower portion, the negative free water clearance is plotted against urine flow. With the onset of diuresis there is an increase in tubular water resorption, which remains fairly constant until maximal flow. Subsequently, a further increase in the resorption of water occurs.

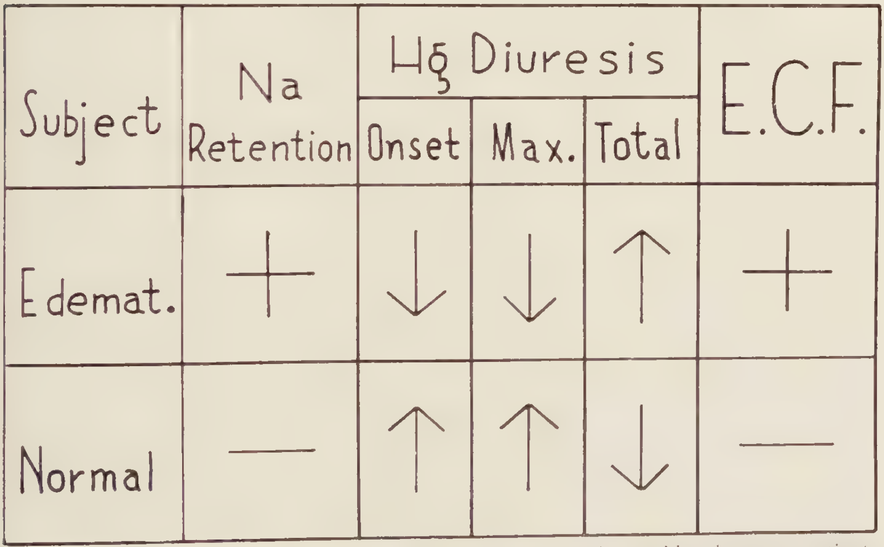
The upper portion demonstrates that, as the volume of fluid passing down the tubule (urine flow (V) + $T^c_{H_2O}$) increases during diuresis, the fraction of water resorbed $T^c_{H_2O}/(T^c_{H_2O} + V)$ anisosmotically falls. As diuresis subsides, this reabsorbed fraction at any given urine flow is increased. (Reproduced by permission from the *Journal of Clinical Investigation.*[19])

creasing urine flow, suggesting that, following maximal diuresis, additional water in excess of solute is again being reabsorbed by the kidney. The fact that this rise in free water clearance is not continuous suggests that the data do not reflect simple accumulation of Pitressin during the study, and that some endogenous antidiuretic mechanism has been activated.

Our interpretation of these data was that the continued loss of extracellular fluid during mercurial diuresis in normal subjects tends to activate mechanisms that normally maintain body fluid volume, thereby leading to increased reabsorption of water and electrolyte and termination of diuresis. Although our observations indicated only that mercurial diuresis ultimately led to increased reabsorption of water, we postulated that mechanisms that increase electrolyte reabsorption are also activated.[19] Subsequently, Bartter *et al.*[20] reported that the highest urinary aldosterone levels observed in normal individuals were found after the extracellular fluid volume had been contracted by mercurial diuretics.

The concept that contraction of extracellular fluid volume in normal subjects leads to activation of mechanisms that terminate mercurial diuresis by increasing renal reabsorption of salt and water is supported by, and helps to clarify, other accepted observations. For example, following the administration of mercurials, normal individuals on regular diets, despite normal renal hemodynamic function, serum electrolyte levels, and much greater urinary sodium and chloride excretion rates, generally exhibit briefer and smaller total diuretic responses than do edematous cardiac patients who, on low-sodium diets with reduced filtration rates, are very actively retaining sodium. The normal subject on a regular diet generally has an earlier onset and a greater maximal rate of diuresis than does the cardiac patient, but the resulting contraction of his extracellular and plasma volumes will soon terminate the diuresis by activating mechanisms that conserve normal body fluid distribution. On the other hand, in the edematous cardiac, although the onset is slower and the maximal rate smaller, the diuresis will continue for a much longer period of time, and the total volume lost is much greater because contraction of the greatly expanded extracellular fluid compartment will actually improve, rather than impair, the circulation (FIGURE 9).

Recently, we have applied this concept in the treatment of patients with massive chronic edema who give only limited responses to the diuretic procedures outlined above. It is a common clinical experience that, in long-standing chronic congestive failure, brawny edema develops, with loss of normal tissue elasticity. It is not surprising that, following diuresis in such patients, despite the persistance of edema, there is a loss of tissue turgor and the same tendency to terminate diuresis that is observed in normal individuals following



Subject	Na Retention	Hg Diuresis			E.C.F.
		Onset	Max.	Total	
Edemat.	+	↓	↓	↑	+
Normal	—	↑	↑	↓	—

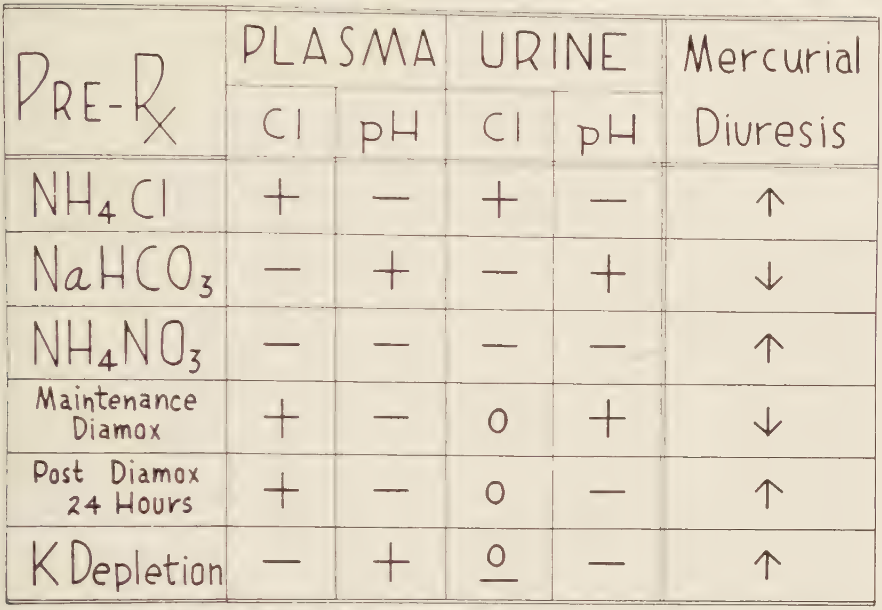
FIGURE 9. Comparison of the mercurial diuretic response observed in edematous patients on low-sodium diets and in normal subjects on regular diets.

diuretic contraction of the extracellular fluid volume. In an effort to overcome this loss of tissue elasticity and to promote the transfer of fluid from the relatively inelastic, chronically edematous tissues to the general circulation, we have instituted the following procedure: once it is established that some diuretic response has been achieved after giving aminophylline two hours following a mercurial, elastic bandages are applied to the edematous limbs from the toes up to the upper thighs. Shortly thereafter, the foot of the bed is elevated to an angle of 30° to 40°. The patient's knees are extended, and he is encouraged to recline with his head and thorax as flat as possible.

This regimen has yielded diureses of 5 to 10 l. in patients who previously were considered only moderately or poorly responsive to the usual therapy with ammonium chloride, mercurials, and aminophylline. However, this procedure must be applied cautiously. First, it should be established that the patient is capable of giving a diuretic response, lest the binding and elevation of the limbs of a patient in whom diuresis has not begun after the administration of aminophylline lead to pulmonary edema due to transfer of fluid from the limbs to the lungs. Second, in some very sick patients a certain amount of edema and expansion of the blood volume may increase the venous pressure, and thereby help to maintain the failing circulation. In such cases, the massive diuresis achieved may, very infrequently, lead to serious difficulties by deluding body mechanisms designed to maintain expanded body fluid to preserve the circulation. Finally, patients who are undergoing massive diuresis must be given an adequate supply of supplementary potassium salts to avert cardiac arrhythmias or other manifestations of potassium depletion.

Although the evidence is clear that mercurial diuresis represents a reversible inhibition of tubular reabsorption of sodium and associated anions, with a consequent osmotic diuresis as indicated above, it is not established whether the primary effect of the mercurial is to inhibit reabsorption of the cation, the sodium, or the anion, chloride. The existence of distal tubular ion-exchange mechanisms that conserve extracellular base provides a satisfactory explanation for the greater diuresis of chloride than of sodium following the administration of mercurials to individuals actively conserving sodium. However, the potentiation of mercurial diuresis by production of ammonium chloride acidosis, which increases the serum chloride level, has been advanced repeatedly as evidence that mercurials must act by decreasing chloride reabsorption. Such potentiation of mercurial response following the administration of ammonium chloride has been reported to persist even after serum-chloride levels have returned to control levels.[4] Moreover, review of the literature suggests that the potentiation of mercurial diuretics by acidifying salts may not depend solely on increase in either serum chloride concentration or urinary chloride excretion.

Recently we tabulated the available information, including some of our own observations, on the effects of various acidifying and alkalinizing procedures on the response of patients to mercurial diuresis (FIGURE 10). In this chart, the increase or decrease in mercurial diuresis produced by certain experimental pretreatment regimens is indicated by the direction of the arrow in the last column, whereas the changes in plasma and urine chloride concentration or



Pre-Rx	Plasma		Urine		Mercurial Diuresis
	Cl	pH	Cl	pH	
NH_4Cl	+	−	+	−	↑
$NaHCO_3$	−	+	−	+	↓
NH_4NO_3	−	−	−	−	↑
Maintenance Diamox	+	−	0	+	↓
Post Diamox 24 Hours	+	−	0	−	↑
K Depletion	−	+	$\underline{0}$	−	↑

FIGURE 10. Relative effects of certain pretreatment schedules on serum and urinary chloride and *p*H, and on mercurial diuretic response.

*p*H, prior to the administration of the mercurial, are indicated by plus or minus signs, representing increase or decrease, respectively. Thus acidification with ammonium chloride produces increase in serum and urine chloride concentrations, decrease in serum and urine *p*H, and augmentation of mercurial diuresis. Conversely, alkalinization following the administration of sodium bicarbonate decreases serum and urine chloride concentration, increases the corresponding *p*Hs, and reduces mercurial diuresis. Acidification with ammonium nitrate, which may decrease serum and urine chloride levels as well as serum and urine *p*H, still potentiates mercurial diuresis. On the other hand, when a patient is given intravenous doses of acetazoleamide (Diamox) on two successive mornings and a mercurial is administered shortly after the second dose of Diamox, the urine *p*H is increased and mercurial diuresis is reduced, although the serum chloride is elevated and the serum *p*H is reduced. Conversely, if a mercurial is given 24 hours after a previous dose of Diamox, the serum *p*H is reduced and the serum chloride level is elevated, as in the previous case, but the urine *p*H is now acid and there is an augmentation of mercurial diuresis. Recently, Mudge and Hardin[illegible] reported that mercurial diuresis is also potentiated in potassium-depleted dogs, the animals developing severe hypochloremic alkalosis but excreting an acid urine (FIGURE 10).

Thus, it would appear that acidification of the urine may be a more critical factor in potentiating mercurial diuresis than is the hyperchloremia or the increased urinary chloride excretion following pretreatment with acidifying agents. Although the mechanism by which increased urinary acidity augments mercurial diuresis is not known, it may be related to changes in the *p*H of renal tubular cells. This supposition suggests that, unless acidification of the urine in the mammalian kidney is not largely a distal tubular function, some mercurial effect on distal tubular processes also may be exerted during the course of potentiated diureses.

Particular attention should be paid to the potentiation of diuresis resulting when the mercurial is given 24 hours after Diamox, in contrast to the inhibition of mercurial diuresis that occurs when Diamox is given shortly before the mercurial. We have applied the former procedure to augment mercurial diuresis in ambulatory and hospitalized cardiac patients, maintained on low-sodium diets and 9 gm. of potassium chloride per day. On 2 successive mornings, single 250- or 500-mg. doses of Diamox are given orally. On the third morning, when the serum chloride is somewhat elevated and the urinary acidity is increased, a mercurial diuretic is given; this is followed 2 hours later by aminophylline, as described above. Another dose of Diamox is administered the next morning, when the serum CO_2 is somewhat increased due to loss of more chloride than sodium during the mercurial diuresis, and again on the following morning. On the succeeding morning, however, Diamox is withheld, and another mercurial is given, followed by an intravenous injection of aminophylline. This therapeutic routine has been effective in patients who find it difficult to take ammonium chloride. It is important, however, to administer the potassium chloride to prevent the development of potassium depletion and hypochloremic alkalosis following the repeated doses of Diamox and mercurials.

Summary and Conclusions

The failure of some cardiac patients to respond to mercurial diuretics has been established to be a late manifestation of the severe retention of salt and water in congestive heart failure. Among the factors contributing to this state whenever cardiac output becomes inadequate for the body's metabolic needs are the following: (1) impaired renal hemodynamics; (2) increased adrenal cortical steroid discharge; (3) alterations in intracellular and extracellular electrolyte and fluid distribution; (4) activation of mechanisms that regulate normal body fluid distribution in an effort to maintain the circulation; and (5) sustained or increased production of antidiuretic hormone. To achieve improved mercurial diuresis, the basic physiological abnormalities must be corrected. In achieving this end, bed rest, adequate digitalization, correction of electrolyte abnormalities, and techniques directed toward maintaining adequate blood volume and circulation, as the extracellular fluid is being rapidly contracted by diuresis, will be of great benefit.

The available evidence suggests that mercurial diuretics doubtless exert an inhibitory effect on a number of proximal tubular functions, including the reabsorption of sodium and associated anions, but it may well be that some distal tubular processes are affected also.

Although, in individuals who are actively conserving sodium, distal-tubular ion-exchange mechanisms that substitute ammonium, hydrogen, and potassium ion for sodium may result in a greater loss of chloride than of sodium, these data do not necessarily support the concept that mercurials act primarily on chloride reabsorption. Similarly, the potentiation of mercurial diuresis by an acidifying agent such as ammonium chloride does not indicate that the changes in serum or urinary chloride concentration are of primary importance in this process. Analysis of the data suggests, rather, that the urinary *p*H at the time of mercurial administration at times is more critical.

Finally, it should be emphasized that, in normal individuals, the reversible inhibition by mercurial diuretics of renal reabsorption of electrolyte leads to a prompt, maximal diuretic response that activates bodily mechanisms that serve to protect extracellular and total body fluid volume by promoting increased renal reabsorption of water and electrolyte. In patients with congestive heart failure, the contraction of extracellular and total body fluids during mercurial diuresis may lead to improved cardiovascular and renal hemodynamics and to the inhibition of some of the mechanisms that had previously been promoting the retention of salt and water, with consequent persistence of diuresis.

References

1. Weston, R. E., D. J. W. Escher, J. Grossman & L. Leiter. 1952. Mechanisms contributing to unresponsiveness to mercurial diuretics in congestive failure. J. Clin. Invest. **31:** 901–910.
2. Stock, R. J., G. H. Mudge & M. J. Nurnberg. 1951. Congestive heart failure. Variations in electrolyte metabolism with salt restriction and mercurial diuretics. Circulation. **4:** 54.
3. Schwartz, W. B. & W. M. Wallace. 1951. Electrolyte equilibrium during mercurial diuresis. J. Clin. Invest. **30:** 1089.
4. Hilton, J. G. 1951. Potentiation of diuretic action of Mercuhydrin by ammonium chloride. J. Clin. Invest. **30:** 1105.
5. Futcher, P. H. & H. A. Schroeder. 1942. Studies on congestive heart failure. II. Impaired renal excretion of sodium chloride. Am. J. Med. Sci. **204:** 52–62.
6. Duggan, J. J. & R. F. Pitts. 1950. Studies on diuretics. I. The site of mercurial diuretics. J. Clin. Invest. **29:** 365–371.
7. Axelrod, D. R. & R. F. Pitts. 1952. Anoxia as a factor in resistance to mercurial diuretics. Am. J. Physiol. **169:** 350.
8. Mudge, G. H. & B. Hardin. 1956. Response to mercurial diuretics during alkalosis: A comparison of acute metabolic and chronic hypokalemic alkalosis in the dog. J. Clin. Invest. **35:** 155–163.
9. Weston, R. E., J. Grossman & L. Leiter. 1951. The effect of mercurial diuretics on renal ammonia and titratable acidity production in acidotic human subjects with reference to site of diuretic action. J. Clin. Invest. **30:** 1262.
10. Pitts, R. F. & O. W. Sartorius. 1950. Mechanism of action and therapeutic use of diuretics. Pharmacol. Revs. **2:** 161–226.
11. Hanenson, I. B., R. E. Weston, J. Grossman & L. Leiter. 1953. Med. Clin. N. Amer. **37:** 643.
12. Weston, R. E., E. R. Borun, J. Grossman, H. A. Guerin, T. D. Ullmann, N. Wolfman & L. Leiter. 1952. Acute hyponatremia due to water retention in congestive heart failure. Proc. Am. Heart Assoc. Sci. **25:** 13.
13. Pitts, R. F., W. D. Lotspeich, W. A. Scheiss & J. L. Ayer. 1948. Renal regulation of acid-base balance in man; nature of mechanism for acidifying urine. J. Clin. Invest. **27:** 48–56.
14. Earle, D. P., Jr. & R. W. Berliner. 1947. Effect of 2,3-dimercaptopropanol on diuresis. Am. J. Physiol. **151:** 215–220.
15. Smith, H. W. 1951. The Kidney Structure and Function in Health and Disease. Oxford Univ. Press. New York, N. Y.

16. Mudge, G. H., J. Foulks & A. Gilman. 1949. Effect of urea diuresis on renal excretion of electrolytes. Am. J. Physiol. **158:** 218–230.
17. Rennels, E. G. & A. Ruskin. 1954. Histochemical changes in succinic dehydrogenase activity in rat kidney following administration of mercurial diuretics. Proc. Soc. Exptl. Biol. Med. **85:** 309–314.
18. Dale, R. A. & P. H. Sanderson. 1954. Observations on the character of mercurial diuresis. Brit. J. Pharmacol. **9:** 210.
19. Grossman, J., R. E. Weston, E. R. Borun & L. Leiter. 1955. Factors influencing the course of mercurial diuresis during Pitressin infusion in normal subjects. J. Clin. Invest. **34:** 1611–1624.
20. Bartter, F. C., G. W. Liddle, L. E. Duncan & C. Delea. 1956. The role of extracellular fluid volume in the control of aldosterone secretion in man. J. Clin. Invest. **35:** 688–689.

THE MODIFICATION OF SODIUM-RETAINING EFFECTS OF A SYNTHETIC STEROID BY A MERCURIAL DIURETIC

By I. J. Greenblatt, G. B. Gordon, and I. Feder
Beth-El Hospital, Brooklyn, N. Y.

Some investigators[1, 2] have contended that a hormonal mechanism is involved in the retention of salt and water in the nephrotic syndrome and in congestive heart failure due to rheumatic-valvular, coronary-artery, and hypertensive heart disease. Recently it has been reported that aldosterone, a naturally occurring steroid, causes sodium retention by its renal-tubular effects.

To explore some of the implications of these observations, we sought to ascertain if, in patients with no known cardiovascular or renal involvement, a hormone can duplicate the salt-retaining effects in these disease states, and whether a mercurial diuretic can overcome this effect.

For this purpose we obtained a quantity of 2-methyl-9a fluorohydrocortisone (the compound U-6683*), a synthetic steroid similar to aldosterone in its inhibitory effect on the excretion of salt, but with about 3 times the potency of naturally occurring aldosterone.[3]

The experimental design consisted of 2 phases. In the first, the steroid, diluted with 250 c.c. of 5 per cent glucose in water, was administered intravenously at a speed of about 10 c.c. min. The U-6683 was given at a concentration of 0.7 μg. kg. of body weight. An indwelling urinary catheter was used to collect urine samples. Blood and urine samples were obtained at periodic intervals and were examined for volume and sodium and potassium output before, during, and after administration of the drug. The second phase duplicated the procedure used in the first, except that a mercurial diuretic was administered intramuscularly in an attempt to overcome the steroid effects.

The subjects of this experiment were a male and a female adult, hospitalized for conditions other than cardiovascular or renal pathology. Both were on 7.5 gm. (estimated) of dietary sodium chloride daily. The female, A.S. No. 35567, weighed 61 kg. The male subject, P.S. No. 35340, weighed 82 kg. TABLE 1 shows the urinary electrolytes for 2 days preceding the tests.

The blood-urea N, Na, Cl, and K were within the accepted limits for normal. On the third day, with the diet still unchanged, and with an indwelling catheter attached to a receptacle, an intravenous injection of 0.7 μg. of the steroid was administered (TABLE 2).

It is apparent from TABLE 2 that a marked inhibition of urinary Na secretion plus a distinct increase in K secretions followed the injection of U-6683. The experiment was repeated 4 days later, following the return to normal of the urine Na and K output but, at the fourth hour, a mercurial diuretic, Mercuhydrin, was administered. The indwelling catheter was omitted, but the technique was unaltered in other respects. As seen in TABLE 3, the results were similar up to the fourth hour but, after the intramuscular injection of 2 c.c. of Mercuhydrin, the renal retention of sodium by i.v. U-6683 was clearly overcome.

---

* Supplied to us through the courtesy of C. J. O'Donovan of The Upjohn Company, Kalamazoo, Mich.

TABLE 1
CONTROL STUDY OF TWO PATIENTS' URINE ELECTROLYTES

Name	Number	Urine vol. 24 Hours	mEq. per liter		Days
			Na	K	
A.S.	35567	1420	68	30	1st 24 hr.
A.S.	35567	1560	79	38	2nd 24 hr.
P.S.	35340	1760	62	40	1st 24 hr.
P.S.	35340	1580	70	49	2nd 24 hr.

TABLE 2
EFFECT OF U-6683 ON URINE VOLUME AND ELECTROLYTES

Subject	Hours	Volume in c.c.	mEq. per liter		Remarks
			Na	K	
A.S. (F)	1	52	31	17	
No. 35567	2	48	26	20	0.7 μg. of U-6683, i.v.
	3	59	20	31	
	4	40	11	60	
	$8\frac{1}{2}$	177	8	76	4-hr. period
P.S. (M)	1	68	46	21	
No. 35340	2	70	40	24	0.7 μg. of U-6683, i.v.
	3	74			
			16	81	pooled specimen
	4	60			
	5 to $7\frac{1}{2}$	243	29	77	3-hr. period

TABLE 3
EFFECT OF U-6683 ON URINE ELECTROLYTES AS MODIFIED BY A MERCURIAL DIURETIC

Subject	Hours	Volume in c.c.	mEq. per liter		Remarks
			Na	K	
A.S. (F)	1 and 2	116	66	31	0.7 μg. of U-6683, i.v. at end of 2 hours
No. 35567	3 and 4	148	19	68	
	5 and 9	906	103	62	2 c.c. Mercuhydrin, i.m. at end of 4 hours
P.S. (M)	1 and 2	131	83	20	0.7 μg. of U-6683, i.v. at end of 2 hours
No. 35340	3 and 4	106	24	59	
	5 and 9	1114	127	50	2 c.c. Mercuhydrin, i.m. at end of 4 hours

Summary and Conclusions

A synthetic steroid, 2-methyl-9α fluorohydrocortisone, caused a marked renal retention of sodium and a high secretion of potassium in the urine of 2 subjects when injected intravenously. Little, if any, change occurred in the secretion of water during the hormonal effects prior to the administration of a mercurial diuretic, Mercuhydrin. The mercurial diuretic overcame the hormonal effects on sodium retention.

These observations suggest, among other implications, that in patients with congestive heart failure who become refractory to mercurial diuretics, the refractoriness might be a function of the increased activity of a hormonal mechanism that negates the diuretic effect of the mercurial. Further work is under way to explore the implications of this hypothesis for the management of congestive heart failure patients, especially patients refractory to mercurial diuretics.

References

1. LUETSCHER, J. A., JR., B. B. JOHNSON, A. DOWDY, J. HARVEY, W. LEW & L. J. POO. 1954. Chromatographic separation of the sodium-retaining corticoid from the urine of children with nephrosis, compared with observations on normal children. J. Clin. Invest. **33:** 276–286.
2. GORDON, E. S. 1955. The role of aldosterone in congestive heart failure. Proc. Cent. Soc. Clin. Research. **28:** 36.
3. O'DONOVAN, C. J. 1956. Personal communication.

BIOASSAY OF ORGANOMERCURIALS

By Theodore H. Greiner*
Cornell University Medical College, New York, N. Y.

Although a substantial part of the pharmaceutical mercury sold in this country is in the form of germicides, this monograph does not include a single paper on that subject. The loss of interest in mercurial antiseptics is due, I believe, to the unfavorable results of bioassay.

Mercury compounds were established as popular antiseptics on the basis of *in vitro* tests: bacteria dipped into mercury solutions would not grow out in culture. Later, however, it was found that virulent bacteria on the skin actually retained their infective capacity after exposure to these antiseptics; assays in which organisms so treated were introduced under the skin showed that they produced infection[1]. As soon as bioassays reflected the actual therapeutic situation, it became clear that there was no special advantage in painting the skin with organic mercurial compounds.

After some years these methods for assay of anti-infective agents attained semi-official status. In *New and Nonofficial Remedies*,[2] the Council on Pharmacy and Chemistry of the American Medical Association stated that, in proposing an antibacterial agent for consideration, it is essential to provide data on its germicidal efficiency under conditions simulating actual use, and they appended a list of references to modified bioassays.

In the 18 years that have elapsed since Price's work,[3, 4] biological assays simulating the demands of clinical practice have overshadowed the earlier *in vitro* tests. Although the mercurial antiseptics retain some popular favor, they are less often employed by physicians.

The results from bioassay of the mercurial diuretic agents are naturally of greater interest today. Assay of diuretic effects in animals has long been used as a screening procedure. Everyone accepts the fact that the information obtained in animal experiments is not necessarily valid for human beings. Even results obtained in the healthy man cannot be assumed to be true for the average patient. Data about the action of the diuretic agents in the patients who will use them are still required. For the most part, these are patients with heart disease and congestive heart failure.

The time-honored system for studying new therapy is the clinical trial. The therapeutic agent under test is added to the usual treatment, and an attempt is made to assess the value of that addition. Results, however, are all too often of the sort quoted by Henry Beecher:[5] "Statement by an eminent clinician: 'I have used the remedy you sent me in several patients. It is my distinct impression that this is the finest thing ever made for the purpose.' " Clinical trials give no assurance that the resulting evaluation will be supported by subsequent experience. There is need for a formal bioassay that includes an estimate of its own error.

Most of the innumerable drugs developed by synthetic chemists and animal pharmacologists in their laboratories have remained untested by physicians. Often the chemicals that do reach clinical trial are those with favorable commercial prospects rather than those having potentially more valuable pharmacological properties.

---

* Present address: Baylor University College of Medicine, Houston, Texas.

What is needed, I think, are methods with which the practicing physician, using only the tools of his own trade, can study the action of drugs and produce results of stated reliability. No elaborate equipment should be required by such methods, and the patient-physician relationship should not be disturbed. Along these lines my colleagues and I have evolved methods for the bioassay of digitalis, hypnotics, antispasmodics, laxatives, and other drugs. None is better established than the assay of diuretic agents in patients with congestive heart failure.[6, 7]

Mention should be made of the development of the diuretic assay for, unlike the assay of surface antiseptics, the diuretic assay has achieved neither wide usage nor official status.

For such a bioassay, we felt that we must choose a response that was related directly and quantitatively to the therapeutic benefit of the diuretic dose and one that could be measured conveniently. The volume of urine flow and the urinary excretion of sodium chloride were not suitable responses; we found it impracticable to require clinic patients to carry several liters of urine to us each week or to keep patients in the hospital long enough to perform an assay.

From the viewpoint of the sick patient the important action of the diuretic agent is the removal of the excess extracellular fluid that is swelling his ankles and filling his lungs. This loss can be recorded as change in weight. The minimum demand made on the patient is that he appear at the clinic on two successive days wearing the same clothes. On the first day he is weighed and receives the diuretic dose. The response is the change in weight by the next day. No technical skill is required, and the necessary equipment is to be found in every outpatient department.

The assay has been performed on patients with congestive heart failure who have been maintained in comfort by diuretic agents for many years. While we have no reason to believe that the potency ratios would not apply also to the hospitalized bedridden patient, we have no evidence on that point.

Over the past 5 years we have encountered no difficulty in maintaining a large and regular group of patients in this assay system; the therapeutic need of the patient is considered in the formal design of the experiment. Each patient is given a dose of diuretic and his response is measured. As soon as the patient returns to approximately his original weight, another dose is administered. Each of the assay doses is given to every patient in a random order. Dosage-response curves are then constructed for each of the compounds and the reliability of the results is tested by the conventional statistical method.

As in all assay systems, the potency is reported in terms of a standard material. Any particular group of patients with congestive heart failure will respond to a given dose with a different weight loss; that is, with a different diuresis. The standard allows the investigator to make comparisons at any time or place. We chose intramuscular meralluride as the standard for several reasons: its chemical structure has been established; various lots have substantially the same composition; and extensive clinical experience has established its efficiency as a diuretic agent. The effect of a new diuretic agent, given in terms of this standard, has a meaning for the practicing physician; it is expressed in terms with which he is familiar.

We have always felt that the major application for this procedure is the rapid evaluation of newly synthesized compounds that have shown a satisfactory diuretic action in animal tests and are therefore candidates for clinical trial. The human assay merely provides a basis for selecting the best candidates and in no sense supplants the formal clinical trial, which alone can sanction general use. Its major function is to avoid fruitless clinical trials, to expose a minimum number of patients to the potential hazard of unknown chemicals, and to focus the attention of medical investigators on the most promising materials.

Considerable interest in this work has been expressed by many clinicians, but the human assay has seldom been used outside our own clinics. Indeed, many of the diuretic agents under investigation pass directly from the animal laboratory to a full-scale clinical trial. We were puzzled by the reluctance of physicians to utilize human assay until a doctor pointed out that he was no mathematician and that he could not follow the statistical verification of the method. It was necessary to verify our method empirically; the procedure was suspect until we had tested a substance of known diuretic potency and had found the correct answer.

We therefore designed an experiment in which the same solution of meralluride served as both the standard and the test preparation. A series of doses of 0.5, 1, and 2 c.c. was designated as the standard, and an identical series as the test preparation. The 6 doses were given in random order. The points in FIGURE 1 represent the average weight loss following the 6 doses. Simple inspection established that for practical purposes the 2 curves were identical; and the correct answer, that the potency of the unknown was the same as the standard, was immediately evident.

When these data were analyzed by statistical procedures, we concluded that the assay was valid; that no differences could be established between the unknown and the standard; that the unknown assayed at 98.9 per cent the potency of the standard; and that, unless the sampling had been upset by a 1-in-20 chance, the true potency of the unknown lay between 80 and 122 per cent of the standard.

We have used this method to evaluate the mercurial diuretics in common clinical use, those accepted for injection by the Council on Pharmacy and Chemistry of the American Medical Association.[2] Several assays were carried out, using intramuscular meralluride as the standard against which all the other preparations were compared. TABLE 1 lists the potency of these compounds in terms of cubic centimeters of the injectable solutions available commercially. The results cluster within a narrow range, with mercurophylline at the top of the series, and mercumatilin at the bottom. The confidence limits for each assay fail to demonstrate any significant difference between the standard and

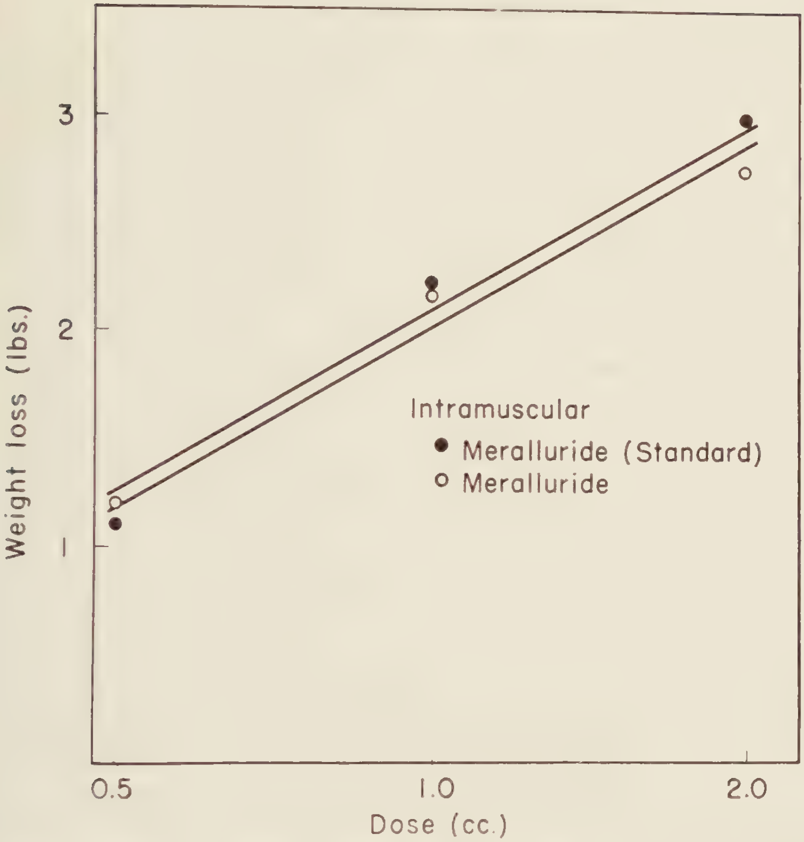


Figure 1. Assay of a "known" diuretic agent in 37 patients with congestive failure. Doses of meralluride assigned as "test preparation" yield the same result as the "standard."

the other compounds tested. The potency of all the intramuscular agents accepted by *New and Nonofficial Remedies* is in the same range, and is entirely satisfactory for all of them.

The commercially available solutions of the common diuretics all contain almost exactly the same concentrations of mercury. Consequently there is very little change in the assay values when they are calculated per atom of mercury. Considering the preparations listed in *New and Nonofficial Remedies*, one might question whether, in congestive heart failure, it is only the dose of *mercury* that counts. To show that this is not true, we have included in the table an assay of chlormerodrin, which is not accepted as an injectable preparation. When administered by the intramuscular route, chlormerodrin obviously had a higher potency per atom of mercury than the other compounds tested.

These assay figures can be applied directly to therapeutic problems. The

TABLE 1

DIURETIC POTENCY OF 6 MERCURIAL COMPOUNDS ASSAYED IN PATIENTS WITH CONGESTIVE HEART FAILURE, COMPARED TO THE STANDARD, INTRAMUSCULAR MERALLURIDE

Drug (intramuscular injection)	No. of subjects	Potency (in volume of solution)		Potency (in molecular weight or mg. of mercury)	
		Potency in % of Standard	Confidence limits at $P = 0.05$	Potency in % of Standard	Confidence limits at $P = 0.05$
Mercurophylline	32	98	79,121	98	79,121
Mercaptomerin	32	90	72,110	88	70,108
Merethoxylline	45	82	62,102	82	62,102
Salyrgan-theophylline	31	77	50,107	75	49,105
Mercumatilin	31	76	49,105	76	49,105
Chlormerodrin	27			250	188,321

doctor treating congestive failure can change from one to another of the six accepted preparations with the assurance that a given dose of one is just as effective as the same dose of another.

Is there any other basis for preference among these 6 compounds? Local reactions, manifested by pain and swelling after single injections and by cumulative nodular formation after a long series of injections, can occur. Data on the incidence of these reactions could be gathered and their significance assessed with experimental designs such as have been used in the past.[8] We have felt that it would not be worthwhile to carry out such studies for all the compounds tested because local reactions are not of critical importance. Such reactions rarely imperil the regimen of treatment and can be handled as they occur by changing diuretics. The incidence of systemic reactions of a serious nature is the only important basis for choice.

No sudden deaths following intramuscular injection have been reported. We have seen no indication of storage of mercury after injection of any of these compounds. Symptoms of overtreatment are the same for all of them. What, then, is the relative rate of occurrence of idiosyncracy or hypersensitivity? How many reactions will occur in 10,000 patients given meralluride or mercaptomerin for a year? A colleague of ours tried to answer these questions by consulting our many thousands of records. Six months later he reported that the task was beyond human endurance.

While attempts to locate all reported reactions to drugs, such as that undertaken by the Committee on Research of the American Medical Association,[9] can tell us how many reactions have been reported, they do not indicate the relative risks of each compound. We should remember that if compound *A* is used 20 times as often as compound *B*, the presence of more reports of the toxicity of compound *A* in the literature does not necessarily indicate a greater risk in its use.

Our bioassay can provide a definitive answer to many a question long disputed among cardiologists; for example, what is the combined effect of ammonium chloride and mercurial diuretics?[10] If no diuretic is given, ambulant patients with congestive heart failure gain a little weight every 24 hours. When loading doses of 8 gm. ammonium chloride were given for 2 days preceding the test period, there was no gain. The slight effect of the ammonium chloride was greatly augmented in the presence of meralluride, an example of true potentiation. In these ambulant patients 2 c.c. meralluride alone could be replaced by 0.8 c.c. meralluride in the presence of ammonium chloride.

On the other hand, xanthine compounds, which are themselves moderately diuretic, had no potentiating effect when given in conjunction with meralluride. There was simple summation of effect in patients who responded to mercurials.[11]

Inferences about the mechanism of action are sometimes drawn from the slope of a dosage-response curve; for example, that compounds with significantly different slopes are not acting at the same receptor site. Approximately the same slope (a loss of 1 lb. in weight each time the dose is doubled) has been found when using mercurial and nonmercurial diuretic agents. The only exceptions to this finding thus far have been the carbonic anhydrase inhibitors; the response to these agents levels off at a maximum of the order of that produced by 0.5 c.c. meralluride.

Another area of dispute that bioassay might clarify is the relative effectiveness of a dose given by various routes of administration. Bioassay of meralluride revealed the effects of intramuscular, subcutaneous, and intravenous injections to be indistinguishable from one another.[12]

This brings us to oral administration, the area of greatest activity in the diuretic field. The history of oral therapy is an ideal source for material with which to document the shortcomings of the clinical trial: practically all the initial clinical tests of oral mercurials have recommended the new agent under consideration, and almost all the agents have subsequently been savagely attacked by the unfortunate men who have tried to use them.

The primary limitation in the use of oral diuretics has been the production of local irritation in the gastrointestinal tract. The relation between diuretic effectiveness and gastrointestinal irritation is the most significant factor to be considered in comparing agents under test for use as oral diuretics.[13]

The measurement of gastrointestinal symptoms is no easy problem. We have found the use of a placebo control, with strict double-blind evaluation of the patient's report, to be the only possible approach. In attempting to gauge the degree of relative irritation, we have used single doses of the compounds large enough to induce toxic effects in about one fourth of the patients. This has been done with full knowledge that various devices, such as divided small doses and rest periods, can be used to reduce irritation. Such schemes can be used in administering all drugs. It is the large single dose, however, that indicates the relative irritant capacity of the agent being tested.

In TABLE 2, the diuretic effectiveness indicated by the assay is cited as the amount of meralluride solution that gives a diuresis equivalent to that following an oral dose of the test compound. "Incidence of toxicity" is the percentage of patients who develop serious toxic symptoms from such doses. The column headed "Relative efficiency" is a rough index that represents the ratio of these 2 values. It is useful for ranking compounds in an array of ascending efficiency.

TABLE 2

EFFICIENCY OF ORAL DIURETIC AGENTS

Drug	Dose (gm.)	Diuretic effectiveness (c.c. meralluride)	Incidence of toxicity (per cent)	Relative efficiency
Meralluride	0.72	0.25	31	81
Aminometradine	0.75	0.61	24	254
Chlormerodrin	0.073	0.71	25	284
Aminoisometradine	1.60	0.56	16	351

It is difficult, however, to be certain that a compound higher on the list is truly better.

In attempting to develop a test of significance, we have tried other ways of combining the 2 variables. Taking the difference between the logarithms of the potency and toxicity is a relatively simple method that also provides an estimate of the variance, and thence a t-test among compounds. As in all indices that combine 2 variables, the error is very large. The last 3 compounds in the table are significantly better than the first, but we have not found any statistically significant differences among these 3 agents. At present, in the hope of increasing the precision of the efficiency index, we are constructing a subjective scale for grading gastrointestinal toxicity.

Chlormerodrin is outstanding among the mercurial diuretics we have tested. Most of the other compounds produce irritation in doses so small as to produce no diuretic effect. Meanwhile, the nonmercurial diuretics have been making great strides. The recently introduced aminometradine ranked almost as high as the mercurial compounds in our assay, and another nonmercurial, aminoisometradine, gave an even better index.

In summary, a system of bioassay representing as closely as possible the therapeutic situation is of great value to rational therapeutics. By means of such a bioassay, mercurial antiseptics have been re evaluated and found wanting. In the case of the mercurial diuretics, some questions about mechanism, potentiation, and route of administration have been answered. From its vantage between the animal test and clinical trial, human bioassay has selected from many series the compound that is now the most prominent oral mercurial diuretic, chlormerodrin (Neohydrin), and its current nonmercurial competitor, aminometradine (Mictine). Whether that achievement was worthwhile depends on one's point of view, but I am certain that rapid return of less effective compounds to the chemist's shelves is not without merit.

References

1. MORTON, H. E., L. L. NORTH, JR. & F. B. ENGLEY, JR. 1948. The bacteriostatic and bactericidal action of some mercurial compounds on hemolytic streptococci. J. Am. Med. Assoc. **136:** 37.
2. AMERICAN MEDICAL ASSOCIATION. 1955. New and Nonofficial Remedies. Lippincott. Philadelphia, Pa.
3. PRICE, P. B. 1938. The bacteriology of normal skin; a new quantitative test applied to a study of the bacterial flora and of the disinfectant action of mechanical cleansing. J. Infectious Diseases. **63:** 301.
4. PRICE, P. B. 1939. Ethyl alcohol as a germicide. Arch. Surg. **38:** 528.

5. Beecher, H. 1953. Clinical impression and clinical investigation. J. Am. Med. Assoc. **151:** 44.
6. Greiner, T., H. Gold, C. I. Bliss, J. Gluck, R. Marsh, S. B. Mathes, W. Modell, H. Otto, N. T. Kwit & L. Warshaw. 1951. Bioassay of diuretic agents in patients with congestive failure. J. Pharmacol. Exptl. Therap. **103:** 431.
7. Greiner, T. & H. Gold. 1952. The clinical assay of diuretic agents. I. Biologic considerations which determine design. Biometrics. **8:** 232.
8. Modell, W., H. Gold & D. A. Clarke. 1945. Quantitative observations on Mercuhydrin and Mercupurin. J. Pharmacol. Exptl. Therap. **84:** 284.
9. Wermer, P. L. 1953. Report to the council. J. Am. Med. Assoc. **152:** 816.
10. Greiner, T., H. Gold, L. Warshaw, R. Marsh, S. Mathes, F. Palumbo, P. Mulrow & N. Kwit. 1953. The value of ammonium chloride as an adjuvant to the mercurial diuretics determined by a bioassay in patients with congestive failure. J. Pharmacol. Exptl. Therap. **108:** 481.
11. Greiner, T., H. Gold, F. Palumbo, L. Warshaw, T. McGowan, J. Weaver & H. Otto. 1955. Bioassay of the diuretic potency of xanthines and the organic mercurials in patients with congestive failure. J. Pharmacol. Exptl. Therap. **113:** 140.
12. Marsh, R., T. Greiner, H. Gold, S. Mathes, F. Palumbo, L. Warshaw & J. Weaver. 1952. A comparison of the diuretic effect of Mercuhydrin (meralluride) administered by several routes. New Engl. J. Med. **247:** 593.
13. Greiner, T. & H. Gold. 1953. Method for therapeutic evaluation of diuretic agents administered orally. J. Am. Med. Assoc. **152:** 1130.

THE ROLE OF MAINTENANCE MERCURIALS IN THE MANAGEMENT OF CHRONIC CONGESTIVE HEART FAILURE*

By John M. Evans

School of Medicine, George Washington University, Washington, D. C.

Current practices of diuretic therapy employing mercury compounds have caused the edematous cardiac drowning in his own dropsy to become largely a problem of the past. Smaller accumulations of edema, however, may be given less attention, and the patient is often permitted considerable latitude in the assurance of dry weight. There are reasons to believe that these smaller accumulations are also detrimental.

The protean influences of chronic heart failure upon the bodily economy are well-recognized. Not only are there disturbances in heart-renal-electrolyte function and pulmonary-gas exchange, but also secondary effects upon the brain, the liver, intestinal absorption, and the general nutritional state. In view of the practicability and safety of maintenance mercurial therapy, it is our purpose to emphasize the importance of keeping the patient with heart failure as fully compensated and as free from edema as possible.

Minor amounts of excess extracellular fluid, when trapped in the pulmonary vascular bed, may be the basis of disturbing restlessness, orthopnea, or nocturnal dyspnea with resulting interference with sleep. Anorexia and nausea, with pain in the right upper abdomen, indicate overloading of the veins of the liver and of the upper gastrointestinal tract, and this condition may be induced by a weight increase as slight as 2 or 3 lb. These symptoms of hepatoportal passive congestion contribute, in some instances, to further reduction in the food intake, which is already impaired by the poor palatability of a diet low in salt and proteins.

It is reasonable to assume that the edema of the gastric mucosa observed in cardiac failure by Palmer and Brick[1] is also present in the small intestine. Available data, although not conclusive, suggest that there is interference with absorption.[2, 3] Moreover, unpublished observations from our laboratory have shown a low, flattened, oral, fat tolerance curve that usually heightens with recovery. The effects of the hypoxia prevailing in the hepatoportal areas may also be significant.[4, 5, 6]

Studies of the serum proteins support the hypothesis that these factors of hypoxia, impaired intake, and absorption contribute to malnutrition.[6, 7, 8] Albumin is frequently low, while globulin may be slightly increased (TABLE 1). Thiamine deficiency is also a common accompaniment of chronic passive congestion, and one may speculate as to the role of intake, absorption, or hepatic metabolism in its etiology.[9, 10] A contributory factor may be the thiamine loss in the urine provoked by mercurial diuresis.[11]

Numerous reports attest to abnormal liver function in congestive heart failure (TABLE 2).[6, 8, 12-16] The liver biopsy studies of Sherlock[17] and of White and

---

* The studies that contributed to this report were supported in part by a grant from The National Heart Institute, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Md.

TABLE 1*

SERUM, ALBUMIN AND GLOBULIN IN 56 PATIENTS

Range in gm. %	Albumin	Globulin
	No. of determiminations	
0 to 0.9	0	0
1.0 to 1.4	2	0
1.5 to 1.9	1	2
2.0 to 2.4	2	8
2.5 to 2.9	10	13
3.0 to 3.4	20	18
3.5 to 3.9	14	9
4.0 to 4.4	5	2
4.5 to 4.9	2	3
5.0 to 5.4	0	1
	56	56

* Reproduced by permission from the *American Journal of Medicine.*

TABLE 2†

INCIDENCE OF ABNORMALITY OF LIVER FUNCTION IN 105 PATIENTS WITH CONGESTIVE FAILURE

Liver Function Test	Group I			Group II			Total		
	Performed (No.)	Abnormal (No.)	Abnormal (%)	Performed (No.)	Abnormal (No.)	Abnormal (%)	Performed (No.)	Abnormal (No.)	Abnormal (%)
Bromsulfalein	55	51	92.7	48	48	100	103	99	96.1
Thymol turbidity	49	20	40.8	44	14	31.8	93	34	36.5
Cephalin flocculation	40	7	17.5	48	17	35.4	88	24	27.2
Serum bilirubin	53	14	26.4	0	0	0	53	14	26.4

† Reproduced by permission from the *American Journal of Medicine.*

TABLE 3‡

IMPROVEMENT IN BROMSULFALEIN EXCRETION AS RELATED TO RESPONSE TO THERAPY FOR CONGESTIVE HEART FAILURE

BSP Excretion	Patients (No.)	Mean BSP on Entry (%)	Mean BSP After Therapy (%)	Patient's response to treatment
Improvement	23	37.2	9.0	All satisfactory
No improvement	7	16.1	22.1	Five patients were refractory to treatment; 1 showed moderate improvement; 1 showed good response.

‡ Reproduced by permission from the *American Journal of Medicine.*

his associates[16] confirm a histopathological counterpart. Also, there is evidence that with return of cardiac compensation the liver dysfunction, as measured by the retention of bromsulfalein, decreases (TABLE 3). There is reason to believe that the hepatic impairment may be important in the nutritional disorders outlined above. In addition, one may postulate the effect upon the retention of salt and water if inactivation of antidiuretic and adrenal cortical hormones is impaired.

These are but a few of the metabolic alterations that accompany failure of the right heart. Additional study will undoubtedly uncover other areas of intermediary metabolism and enzyme function that are rendered inefficient. In any event, there is every reason to believe that full compensation is beneficial to the cardiac patient, to his sense of well-being, and to his effective bodily economy.

Is it possible to accomplish this objective with the currently available therapeutic measures? The answer for most patients is an emphatic "yes." Full digitalization is assured by the usual well-defined approaches. Dietary sodium is restricted by careful instruction and, often, with the aid of the dietitian. It is important to realize that, even with good cooperation, there is usually a protective sodium chloride "cushion" of 3 to 6 gm. per day. If these and other general measures are ineffective, one turns to the potent diuretics. Carbonic anhydrase inhibitors have a place in the milder instances of failure. My associates and I have found them of less value in the more advanced cases.[18]

In subjects with more advanced failure, usually after initiation of diuresis with parenteral mercurials, the ambulatory patient is placed on a regimen of maintenance oral mercury in the dose necessary to assure freedom from symptoms and absence of edema as determined by weight. Ideally, weighing is done at home before breakfast every other day, and shifts of 2 or 3 lb. are reported to the physician for adjustment of dosage. The frequency of mercury administration varies, from daily to 4 or 5 days per week, the required amounts being given in single or divided doses. Since a deficit of chloride will interfere with mercurial effectiveness, most patients should receive 3 to 6 gm. of ammonium or potassium chloride in divided doses 4 to 7 days per week. Although decompensated hyperchloremic acidosis and "ammonia intoxication" are potential hazards and should be watched for, they are rarely seen. A daily ration of a balanced multivitamin preparation containing 5 to 10 mg. of thiamine is provided to prevent deficiency.

Patients should be followed in accordance with the severity of their illness but, in most instances, a visit to the physician every 2 to 6 weeks suffices. At that time they are reviewed for such possible side effects as stomatitis, gastrointestinal disturbances, or dermatitis, and for indications of electrolyte imbalance, to be confirmed by suitable biochemical determinations. Urine should be examined periodically along with blood urea nitrogen, particularly in those patients with a component of primary renal disease.

A gain of more than 3 to 5 lb. in weight, or the appearance of symptoms, signals a "breakthrough" in the program. In their approximate order of frequency, failures of treatment can be attributed to dietary excesses of sodium, respiratory or other infections, chloride deficit or hypochloremic alkalosis, digitalis intoxication, carditis in the rheumatic cardiac, altered renal function or, rarely, hyponatremia. Treatment is directed at the cause of the breakthrough. If none is present, the dose of tablet mercury is increased appropri-

TABLE 4*

ETIOLOGIC DIAGNOSIS OF THE 38 PATIENTS STUDIED

Diagnosis	No. of subjects
ASHD	15
HASHD	14
RHD	5
SHD	2
Interauricular septal defect	1
Nonspecific myocarditis	1

Definitions: ASHD—arteriosclerotic heart disease; HASHD—hypertensive arteriosclerotic heart disease; RHD—rheumatic heart disease; SHD—syphilitic heart disease.

*Reproduced by permission from *The Annals of Internal Medicine.*

TABLE 5

COMPOSITION OF THE SERIES

(1) Females, 21—males, 17
(2) Age range, 27 to 76 years
(3) Functional classification, II to IV (New York Heart Association).
(4) Duration of treatment, 8 to 84 weeks; average, 38 weeks.
(5) Dose range, 2 to 12 tablets; average, 2.7 day

ately, or supplementary 1- to 3-ml. injections of mercury are given until "dry weight" is achieved once more. With complications or continued inadequacy of the program, the patient must be admitted to the hospital for readjustment of dietary intake, digitalis, electrolytes, and for other methods of treatment as adequate diuresis is restored.

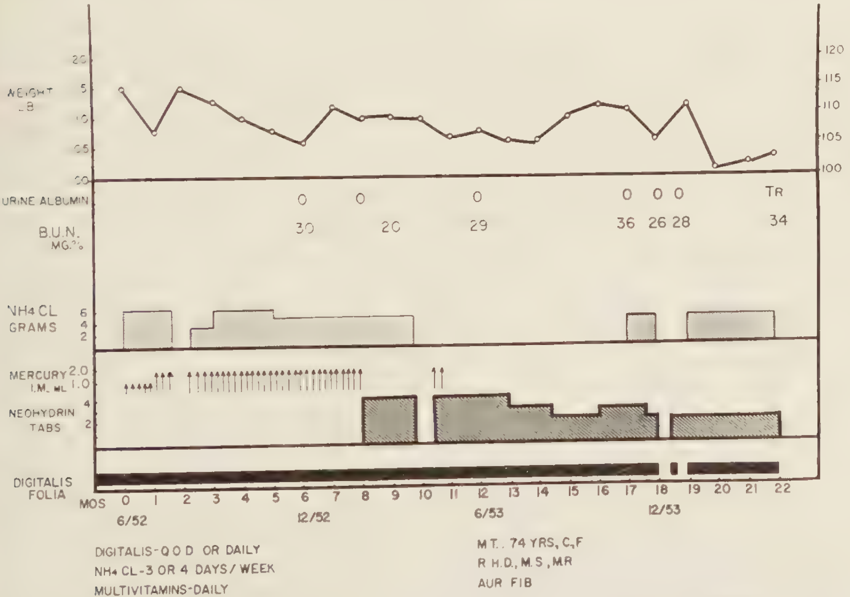


FIGURE 1. The results of treatment in patient M. T., with good response.

TABLE 6

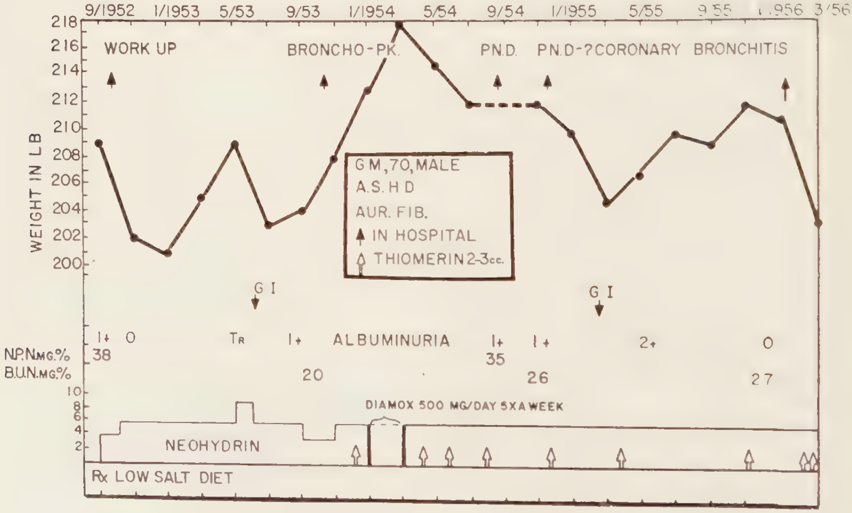
REACTIONS DURING ORAL THERAPY: 38 SUBJECTS

(1) Gingivitis or stomatitis	6	
(2) Gastrointestinal symptoms: nausea and emesis, pain or cramps	2	
(3) Dermatitis	2	
Total	10	of 38—26.3%
Reactions requiring discontinuation	8	of 38—21.1%

Another source of failure of the program originates in the more severe states of cardiac decompensation, class IV (New York Heart Association, New York, N. Y.), where absorption of oral mercurials probably is impaired. These patients need parenteral mercury in doses of 1 to 3 ml. titrated in accordance with their need as outlined above. The injections may be self-administered at home by the intelligent patient, or given by a visiting nurse or member of the family.

To illustrate certain features of this approach to maintenance-mercurial therapy, the following patient study is reported in brief:[19]

Thirty-eight patients with chronic heart failure (classes II to IV) were selected from the Cardiac Clinic. The etiological diagnosis and composition of the series of 38 patients are shown in TABLES 4 and 5. Without other changes in the regimen, an oral mercurial (Neohydrin) was substituted for parenteral mercury and given daily for periods up to 84 weeks. Twenty-six of the 38 patients (68.4 per cent) were able to continue on the drug without reactions and with good control of the failure on an average dose of 2.7 tablets per day.



DIGITALIS FOLIA 0.1 GM. DAILY OR Q.O.D. MULTIVITAMINS 1-2 CAPS. DAILY
NH_4CL GMS. 3-6 4x A WEEK OR DAILY NEOHYDRIN Q.O.D., OR IN ALTERNATE WEEKS
P.N.D.=PAROXYSMAL NOCTURNAL DYSPNEA G.I.=GASTROINTESTINAL SYMPTOMS

FIGURE 2. Summary of 42 months of treatment in a patient showing the absence of renal intoxication as measured by aggravation of nitrogen retention or albuminuria.

TABLE 7

RESULTS OF ORAL MERCURY TREATMENT: 38 SUBJECTS

(1) Good control	26 of 38—68.4%
(2) Discontinuance due to reaction	8 of 38—21.1%
(3) Inadequate control	4 of 38—10.5%

FIGURE 1 shows graphically the results in patient M. T. with a good response to treatment. Eight to 12 tablets per day were tolerated for short periods in certain patients. The drug was discontinued in 8 of the 38 subjects (21.1 per cent) because of side effects. As shown in TABLE 6, the reactions included gingivitis or stomatitis in 4, dermatitis in 2, and gastrointestinal symptoms in two. Renal intoxication, as measured by an aggravation of the retention of nitrogen or by albuminuria or hematuria, was absent. FIGURE 2 presents the results in a patient, not in this series, treated for 42 months without evidence of renal intoxication. Inadequate diuresis was observed in 4 of the subjects (10.5 per cent) with severe heart failure (class IV), fixed hepatomegaly, and ascites, in which absorption of mercury may be impaired. These results are summarized in TABLE 7.

It was noted that many of the patients achieved a lower outpatient weight in contrast to that obtained by intermittent parenteral dosage. Most patients preferred the oral treatment program, and all were freed of postinjection symptoms. It should be emphasized that gastrointestinal complaints due to hepatoportal congestion may be confused with drug irritation and are often relieved by increased doses of the diuretic as the gut and liver are unburdened of edema.

The careful application of a program of maintenance mercurials in cardiac therapy decreases symptomatology, promotes well-being, and adds not only years to life, but life to years, as well. Many patients are enabled to resume their former occupations part or full time and to return to economic independence. The frequency and duration of hospitalizations are decreased with a reduction in the economic burden upon the individual and the community.

Conclusion

In conclusion, let me emphasize the fact that the use of mercurial diuretics in a program of maintenance therapy has been shown to be practicable, effective, and reasonably safe in the ambulatory patient with mild to moderately severe congestive heart failure. The assurance of "dry weight" and the fullest possible cardiac compensation adds to well-being and reduces the secondary effects of passive congestion upon the general bodily economy.

References

1. PALMER, E. D. & I. B. BRICK. 1955. Esophageal varices: causes other than cirrhosis and portal-vein block. J. Am. Geriatrics Soc. **3:** 681.
2. MCMICHAEL, J. & F. H. SMIRK. 1933. The effect of experimental portal congestion on the absorption and excretion of water. J. Pathol. Bacteriol. **37:** 81.
3. WELLS, H. S. 1940. The balance of physical forces which determine the rate and direction of flow of fluid through the intestinal mucosa. Am. J. Physiol. **130:** 410.
4. VAN LIERE, E. J. 1942. Anoxia. Its effect on the body. Univ. Chicago Press. Chicago, Ill.

5. Myers, J. D. & J. B. Hickam. 1948. An estimation of the hepatic blood flow and splanchnic oxygen consumption in heart failure. J. Clin. Invest. **27:** 620.
6. Evans, J. M., H. J. Zimmerman, J. G. Wilmer, L. J. Thomas & C. B. Ethridge. 1952. Altered liver function of chronic congestive heart failure. Am. J. Med. **13:** 705.
7. Payne, S. A. & J. P. Peters. 1932. The plasma proteins in relation to blood hydration. VIII. Serum proteins in heart disease. J. Clin. Invest. **11:** 103.
8. Felder, L., A. Mund & J. G. Parker. 1950. Liver function tests in chronic congestive heart failure. Circulation. **2:** 286.
9. Robinson, W. D., D. Melnick & H. Field, Jr. 1940. Urinary excretion of thiamine in clinical cases and the value of such analyses in the diagnosis of thiamine deficiency. J. Clin. Invest. **19:** 399.
10. Wohl, M. G., C. R. Shuman, R. Turner & J. J. Fittipolli. 1953. Thiamine deficiency in organic heart disease. Circulation. **8:** 744.
11. Williams, R. H. & G. W. Bissell. 1944. Thiamine metabolism with particular reference to the role of the liver and kidneys. Arch. Internal Med. **73:** 203.
12. Jolliffe, N. 1929–1930. Liver function in congestive heart failure. J. Clin. Invest. **8:** 419.
13. Cantarow, A. 1935. Studies of hepatic function. II. In portal cirrhosis and congestive heart failure. Arch. Internal Med. **56:** 521.
14. Bernstein, M., E. G. LeWinn & S. Simkins. 1942. Heart disease and liver function. J. Lab. Clin. Med. **28:** 1.
15. Chavez, I., B. Sepulveda & A. Ortega. 1943. The functional value of the liver in heart disease. An experimental study. J. Am. Med. Assoc. **121:** 1277.
16. White, T. J., C. M. Leevy, A. M. Brusca & A. M. Gnassi. 1955. The liver in congestive heart failure. Am. Heart J. **49:** 250.
17. Sherlock, S. 1951. The liver in heart failure. Relation of anatomical, functional and circulatory changes. Brit. Heart J. **13:** 273.
18. Massumi, R. A. & J. M. Evans. 1955. Studies on the continuous use of a carbonic anhydrase inhibitor (Diamox) in ambulatory patients. Am. Heart J. **49:** 626.
19. Evans, J. M. & R. A. Massumi. 1956. The long term use of the oral diuretic 3-chloromercuri-2 methoxy-propylurea (Neohydrin) in ambulatory patients. Ann. Internal Med. **44:** 124.

THE OUTPATIENT MANAGEMENT OF THE CARDIAC PATIENT WITH MERCURIAL DIURETICS

By William E. Lawrence and Margaret S. Klapper
Department of Medicine, Medical College of Alabama, Birmingham, Ala.

The importance of diuretic therapy in the management of congestive heart failure is well established, and the organic mercurial diuretic compounds are now accepted as standard agents in the treatment of this condition. The intensive mercurial therapy required for the edematous patient in acute congestive heart failure is usually performed under controlled hospital conditions. The maintenance of compensation in the outpatient with chronic heart failure, however, may present a somewhat different problem in management. There is a precarious balance between failure and compensation in most patients suffering from this ailment; and the maintenance of the compensated state depends, for the most part, on careful adjustment of diuretic dosage. The fluctuations in diuretic requirement may frequently demand that the treatment of the outpatient be controlled as carefully as that of the hospitalized acutely ill patient.

It is a common observation that many patients, after recovery from acute congestive heart failure, show continued improvement without diuretics and can be maintained for long periods on digitalis alone. This can be expected in patients who have had mild initial failure, or who have had failure secondary to reversible myocardial changes. Our outpatient clinic has included an average of 60 to 80 class III and class IV cardiac patients for the past 6 years; and it has been our experience that such patients usually cannot be maintained in a compensated state without a regular and frequent administration of mercurial diuretics.

Sixty of these patients were given a placebo instead of a standard mercurial diuretic.[1] In addition to digitalis, all of them had received regular mercurial therapy for periods of 6 months to 5 years, and they were in a compensated state on this regimen. Eighty per cent (49) of these patients reverted to obvious congestive heart failure following the withdrawal of mercurials. The onset of failure occurred after intervals of 5 days to 17 months; 60 per cent (36) reverted in less than 3 months, and 75 per cent (48) in less than 6 months. Resumption of mercurial therapy resulted in the prompt return of each individual to compensation.

It appears from these results that a large majority of patients with chronic congestive heart failure cannot be maintained without mercurial diuretics. The fact that textbooks of medicine continue to devote considerably more space to digitalis than to mercurial diuretics makes one doubt that the importance of diuretic treatment in heart failure has received proper emphasis.

Until recently, mercurial therapy by the parenteral route was the only reliable method of obtaining adequate diuresis in patients with congestive heart failure.[2-7] The introduction of Neohydrin appeared to us to offer the promise of an alternative to the commonly used parenteral preparations.[8-11] We therefore incorporated this drug into our program of management and found that approximately 65 per cent of the outpatients who had previously required Mercuhydrin at weekly or more frequent intervals could be maintained in a compensated state with Neohydrin as the only diuretic. This performance by an oral diuretic has been unmatched in our experience.[1, 12, 13]

Side effects attributable to the drug have been minimal. The most common side effects noted in patients receiving Neohydrin are occasional minor gastrointestinal disturbances.[1, 6, 14] Twenty-four per cent of our patients receiving Neohydrin have reported such complaints from time to time, but the symptoms were not of sufficient severity to necessitate discontinuance of the drug. It is of interest that the same symptoms were reported, but to a slightly smaller extent, when the same patients were receiving a placebo. Sensitivity to mercury, manifested by gingivitis, stomatitis, or dermatitis, may occur during the course of Neohydrin therapy.[1, 6, 14] However, such manifestations prompted us to discontinue the drug permanently in only 3 patients. The symptoms of sensitivity disappeared completely upon withdrawal of the drug. Oral sensitivity has not occurred in patients with good oral hygiene.[1, 15]

Patients with chronic congestive heart failure show certain peculiarities not ordinarily encountered in the management of other illnesses. Regardless of the etiology of the cardiac disorder, there is a common denominator that differentiates these patients from other chronically ill individuals. This shared factor is the tendency of these patients to develop fluid and electrolyte retention, with concomitant development of dyspnea of varying degrees of severity. These patients are likely to experience relief when the water and electrolyte balance is restored.

In general, our plan of management employs a conventional regimen. Treatment with digitalis is maintained in all patients. A low-sodium diet is prescribed, and its importance is emphasized. These basic measures are accompanied by the regular and intensive administration of mercurial diuretics. Mercuhydrin, parenterally administered, is used initially, and it is given daily until maximal compensation is attained. Neohydrin is then administered, usually in doses of 3 tablets daily, and this dosage is adjusted according to the clinical response. Due to an occasional lag in the diuretic effect of Neohydrin, Mercuhydrin is continued in the usual dosage for a week or two after the administration of Neohydrin has been initiated. The average effective dosage of Neohydrin in our patients is 3 to 4 tablets daily. The patient whose requirement is greater than 6 tablets daily will usually require supplementary Mercuhydrin.

The generally accepted clinical criteria are used in evaluating the state of compensation and in adjusting the dosage of diuretic. In the patient with chronic congestive failure, the appearance of the earliest indications of impending failure calls for immediate intensification of therapy. Increased exertional dyspnea, paroxysmal nocturnal dyspnea, and orthopnea are considered the most reliable early symptoms. Rales in the lungs and demonstrable edema are pathognomonic, but they usually follow the appearance of the symptoms listed above. Changes in body weight have been described as the best single guide to adjustment of diuretic dosage. Although this sign is admittedly of primary importance in certain patients, loss or gain in weight is not always a reliable sign of change in the degree of compensation. In fact, it is not unusual for a patient to lose weight while gradually reverting to failure and to gain true weight while returning to a state of compensation. A possible explanation is that slowly increasing failure may be associated with loss of appetite and a decrease in body weight that is out of proportion to fluid accumulation; conversely, the patient who is attaining compensation may enjoy an improved appetite and gain actual body weight. We have previously reported a study of 39 patients who were allowed to revert to clinical heart failure by the omission of diuretics; the average gain in body weight of these individuals was not statistically significant.[12, 16] Our patients, therefore, are instructed to return for immediate re-evaluation and adjustment of diuretic dosage as soon as early symptoms of impending failure appear.

Outpatients on maintenance therapy with mercurial diuretics are observed carefully for evidence of electrolyte imbalance. None has exhibited the clinical picture of the "salt-depletion" syndrome or the spontaneous "redigitalization" phenomenon. Approximately one tenth of the patients who require injections for maintenance have reported mild muscle cramps or weakness a few hours after injections. There has been no laboratory evidence of hyponatremia, hypochloremia, or hypokalemia, whether the patients have received oral therapy alone or in combination with parenteral therapy. We have not observed significantly altered levels of these electrolytes in a single patient on maintenance therapy. It is possible that the results we have observed are due partly to the inability of some of our patients to adhere to a rigidly controlled diet and partly to our policy of not using enhancing agents or other diuretics with the mercurials in trying to keep the maintenance regimen as simple as possible.

The presence and extent of concurrent renal damage in patients with chronic congestive heart failure may be difficult to ascertain with any degree of accuracy. The findings of albuminuria, casts, low specific gravity of urine, and elevated blood urea nitrogen (B.U.N.) are common to both conditions. The average age of our patients is 65 years, and it is likely that many of them have extensive renal impairment. We follow the generally accepted view that there are few contraindications to the use of mercurials in patients with congestive heart failure, regardless of the state of the kidneys.[3, 6, 7]

Even when chronic renal impairment is known to exist, it has been our experience that when congestive heart failure is controlled, the urines tend to become clear and the blood urea nitrogens (B.U.N.) to return toward normal amounts. During the treatment, it is our policy by frequent blood chemical analyses to observe carefully those patients with B.U.N. above 40 to 50. In the presence of a rising B.U.N., caution pertaining to amount and frequency of mercurial administration is exercised. Administration of the drug may be discontinued temporarily until it is ascertained whether the deterioration of the patient is more rapid without the diuretic than with it.

In conclusion, we have found that, once the necessity for diuretics has been established in patients with chronic congestive heart failure, this need will continue indefinitely or permanently in at least 80 per cent of the cases. Approximately 65 per cent of these patients can be maintained with Neohydrin as the diuretic. A regimen of diet, digitalis, and mercurial diuretic administration may be applied to outpatients who are class III and class IV cardiac patients. This maintenance program may be continued for months and years without undue risk of electrolyte imbalance or mercurialism. The resultant increase in longevity is associated with an improved ambulatory status and an increased sense of well-being.

References

1. Lawrence, W. E., S. S. Kahn & A. B. Riser. 1954. A comparative study of the clinical effects of oral and parenteral mercurial diuretics in 70 patients with congestive heart failure. Southern Med. J. **47:** 105.
2. Gold, H., T. Greiner, S. B. Mathes, R. R. March, L. J. Warshaw, W. Modell, N. T. Kwit, H. L. Otto, S. Garb, H. Bakst & M. L. Kramer. 1952. Study of the mercurial diuretic, Thiomerin (mercaptomerin), by subcutaneous injection in patients with congestive failure. Am. J. Med. Sci. **223:** 618.
3. Gold, H., N. Kwit, W. Modell, L. W. Hanlon, M. Kramer, S. Greenberg, H. Otto, E. Cotlove, A. Benton, M. Pearlmutter & W. Zahn. 1947. A system for the routine treatment of the failing heart. Am. J. Med. **3:** 665.
4. Goldring, W. 1946. Cornell Conferences on Therapy. The use of the mercurial diuretics. N. Y. State J. Med. **46:** 62.
5. Riser, A. B., S. S. Kahn, W. O. Pardue, & W. E. Lawrence. 1951. Mercurial diuretics in the treatment of congestive heart failure. Am. Practitioner and Dig. Treatment. **2:** 15.
6. Vogl, A. 1953. Diuretic Therapy. Williams & Wilkins. Baltimore, Md.
7. Vogl, A. 1955. The use of mercurial diuretics in congestive heart failure. Mod. Conc. cardiov. Dis. **24:** 263.
8. Finch, G. H. 1952. Clinical investigation of tablet Neohydrin, a new oral mercurial diuretic. J. Iowa State Med. Soc. **42:** 490.
9. Greiner, T. & H. Gold. 1953. Method for therapeutic evaluation of diuretic agents administered orally. J. Am. Med. Assoc. **152:** 1130.
10. Moyer, J. H. & C. A. Handley. 1952. Clinical diuretic studies on three new mercurial compounds. Federation Proc. **11:** 378.
11. Nuhfer, P. A. & S. White. 1951. A study concerning orally active mercurial diuretics. J. Pharmacol. Exptl. Therap. **101:** 30.
12. Klapper, M. S. & W. E. Lawrence. Unpublished data.
13. Lawrence, W. E., S. S. Kahn & A. B. Riser. 1954. A comparative clinical study of two oral mercurial diuretics. Clin. Research Proc. **2:** 131.
14. Brown, E. A. 1955. The question of reactions to mercurial diuretics. Ann. Allergy. **13:** 131.
15. Evans, J. M. & R. A. Massumi. 1956. The long term use of the oral diuretic 3 chloromercuri-2-methoxy-propyl-urea (Neohydrin) in ambulatory patients. Ann. Internal Med. **44:** 124.
16. Kahn, S. S., W. E. Lawrence & M. S. Klapper. 1954. Body weight changes in thirty-nine patients with congestive heart failure following withdrawal of mercurial diuretic therapy. Clin. Research Proc. **2:** 120.

LONG-TERM ORAL MERCURIAL DIURETIC THERAPY IN CONGESTIVE HEART FAILURE

By George C. Griffith and Edward M. Butt

Departments of Medicine (Cardiology) and Pathology, University of Southern California School of Medicine and the Los Angeles County Hospital, Los Angeles, Calif.

Control of congestive heart failure in patients who otherwise do not require close medical supervision has been improved and simplified with the development of efficient oral mercurial diuretics. These permit easy, continuous maintenance of an edema-free state without either the necessity for frequent injections or the discomfort of the intermittent edematous periods that are unavoidable with the parenteral administration of diuretics at widely spaced intervals. A number of effective and relatively nontoxic oral organomercurial preparations have been developed: among others, Cumertilin (mercumatilin), Mercuital, Merpurate, and Neohydrin. In the outpatient cardiac clinics of the Los Angeles County Hospital, Los Angeles, Calif., we have administered Neohydrin to 23 adult patients with congestive heart failure over periods of 20 to 65 months, without incident—convincing evidence of the practicability of long-term therapy with oral organomercurials.

Advantages of Oral Administration

Judging by reports in the literature and by our own experience with Neohydrin, few untoward reactions are associated with the administration of oral organomercurials to patients free of significant renal disease. The rarity of side reactions is due in large part to the constancy of control involved in the daily administration of an oral diuretic, as contrasted with necessarily more intermittent parenteral injections. I emphasize the fact that we do not use oral preparations to produce the initial diuresis, but restrict their use to maintenance of an edema-free state following the "drying out" period. Daily use of organomercurials prevents the build-up of edema and avoids complications that might occur when the markedly edematous patient is subjected to rapid diuresis.

Slow, regular diuresis is less apt to cause marked alterations in fluid and electrolyte balance—the common complications of diuretic therapy. Massive, intermittent diuresis is particularly hazardous to the diabetic patient, whose labile potassium balance is easily disturbed and who may lose significant amounts of this ion following large doses of parenterally administered mercurials.*

Oral organomercurial therapy is particularly well suited for the control of congestive failure in children because it produces continuous diuresis without dreaded injections, and because it permits an adequate diet containing generous amounts of nutrients.

The occasional patient who suffers leg pains or skin eruptions following the parenteral administration of organomercurials is spared these discomforts when mercurials are administered orally.

---

* Control of congestive heart failure in the diabetic patient poses a peculiar problem, as the edema itself may make the diabetes milder and may even return the blood sugar to normal. In these patients, relief of the edema may cause a recurrence of glycosuria.

Drawbacks of Oral Administration

The use of oral organomercurials also has drawbacks and contraindications. When drugs are administered orally, we may expect poor absorption in the presence of congested viscera, or of nausea, vomiting, or other gastrointestinal complaints. If active gastrointestinal lesions -ulcers, or perhaps gastritis– are present, even the slight irritation produced by the oral diuretic may aggravate symptoms of the lesion. One must use parenteral injections in such cases. Stomatitis, gingivitis, or toothache may become a problem unless meticulous attention is paid to oral hygiene. One case of subacute mercurialism has been reported;[1] this finding is surprising because the oral mercurials currently in use are organic compounds that contain no freely ionizable mercury.[2]

Conditions that make close and constant observation of the patient necessary are usually controlled more successfully with parenteral administration. Examples of such conditions are: rapidly progressive cardiac failure; or repeated accumulation of so much edema fluid in a pleural cavity or in the abdominal cavity that mechanical removal is necessary (the "sump" phenomenon*).

As with the administration of mercurial preparations by intravenous, intramuscular, or subcutaneous routes, the most important contraindications to oral mercurial diuretic therapy are uremia and the presence of significant primary renal disease. Nevertheless, evidences of renal passive congestion, such as elevated nonprotein nitrogen (N.P.N.) values or moderate albuminuria, do not in themselves contraindicate organomercurial administration, as the observed renal congestion may be secondary to the cardiac decompensation. In patients whose renal failure is secondary to congestive heart disease, elevated N.P.N. values usually rise again for a brief interval after the initiation of therapy because of hemoconcentration and then return to within normal limits as the congestive failure is brought under control and the resultant renal congestion is relieved. As a rule, we regard N.P.N. values of 60 mg. or more per 100 c.c. as suggestive of primary renal disease, and we withhold organomercurial therapy from patients with N.P.N. values of over 70 mg. until the possibility of renal disease has been investigated.

Results of Study

We have studied the effects of the administration of Neohydrin to 23 patients with congestive heart failure. Treatment was continued for periods of from 20 to 65 months. The patients studied were between the ages of 32 and 81. All were in class III, C or D, according to the classification of the American Heart Association, New York, N. Y., and they had previously received a parenterally administered organomercurial (Mercuhydrin) to promote the initial loss of edema. Some of the patients had been maintained for varying

* Despite the use of mercurials, sodium loss through the kidneys in patients who manifest the "sump" phenomenon is relatively minor; however, in a few instances, removal of edema fluid from the abdominal cavity will trigger the desired diuresis by relieving the kidneys.

periods on Mercuhydrin before the oral diuretic was substituted. The majority of the patients suffered from arteriosclerotic heart disease, although a considerable number of them had inactive rheumatic heart disease and several had hypertension or cor pulmonale. The dosage of Neohydrin (1 to 4 tablets per day, containing 10 mg. organic mercury each) was adjusted to the need of the individual patient and was varied according to changes in cardiovascular status. At the beginning of this study, the patients were seen at weekly intervals but, as efficacy of the drug and tolerance to it were confirmed, intervals of 4 weeks or more were permitted to elapse between visits.

Criteria used in evaluating the effectiveness of the drug included: maintenance of "optimal weight"; continued reduction or absence of rales, peripheral edema, and hepatomegaly; and subjective improvement. Rather than attempt to maintain the patient at "dry weight," which is actually a state of mild dehydration with attendant discomforts and weakness, we sought to keep him at his "optimal weight," that at which he appeared best clinically and was most comfortable.

Although 12 of the 23 patients had high nonprotein nitrogen values or albuminuria, or both, at the onset of treatment, none suffered clinically evident damage as a result of prolonged treatment with Neohydrin. High nonprotein nitrogen levels present at the beginning of therapy dropped to normal or near-normal levels as congestive failure was brought under control. The N.P.N. value of one patient dropped from 96 mg. to 40 mg.; the N.P.N. value of a second patient, from 80 mg. to 40 mg.—a strong indication that nitrogen retention in these patients was due to circulatory changes secondary to cardiac failure. In several patients, nausea and vomiting present at the beginning of the therapy cleared after compensation was restored. Small amounts of albumin continued to appear in the urine of some patients. Histological study of the kidneys of the one patient who died during the study showed no tubular damage and, except for indications of passive congestion, the kidneys were normal in every way.

Discussion

In the treatment of patients with congestive heart disease, maintenance of an edema-free state is second in importance only to adequate support of the myocardium with digitalis. In some patients (children or adults) with indications of active rheumatic disease, for whom digitalis is of little value and may actually be harmful, promotion of adequate diuresis is of paramount importance. Our results indicate that patients with congestive heart disease can be maintained satisfactorily over long periods with oral organomercurials. Most patients are encouraged by the substitution of oral therapy for the injections, but a few who have developed psychic dependence upon the injections require adequate reassurance at the time of transition.

The regimen followed by our patients has been as follows: complete digitalization, moderate sodium restriction, rest commensurate with disability, and the minimum dosage of organomercurial that will promote diuresis. When there is a tendency toward hypochloremic alkalosis, patients receive prophylactic doses of ammonium chloride (4 to 6 gm. daily) during the period of organomercurial administration. In patients with cor pulmonale, acetazoleamide (Diamox) is helpful in raising serum chloride levels. Efficacy of diuretic action apparently is dependent upon proper fluid and electrolyte balance—especially upon sufficient supplies of chloride—and we attempt to maintain the *p*H of the urine at about 5.5. Refractoriness to organomercurial therapy in patients who formerly responded satisfactorily can be traced to sodium depletion, hypochloremic alkalosis, or—in patients whose kidney tubules have lost the ability to reabsorb selectively from the glomerular filtrate sufficient potassium to maintain potassium balance—hypokalemia. The clinical symptoms of these conditions overlap, and 2 or all may coexist in the patient; electrolyte determinations will indicate corrective treatment. If the patient's serum calcium happens to be low when diuresis is instituted, the subsequent drop in serum calcium may give rise to symptoms of latent tetany. With diuresis induced by daily administration of oral mercurials, reactions are less likely to occur than with parenteral injections. In a few instances, severe hypoproteinemia may diminish or block the response to the mercurials. In these patients, diuretic response is increased considerably by prior administration of plasma or serum albumin. Adjustments in dosage are required in response to changes in the patient's status or, in summer, because of excessive sodium loss through perspiration. Upward adjustments may be required temporarily because of the failure of the patients to adhere to dietary restrictions.

Occasional reports in the literature suggest that the number of gastrointestinal upsets increases with larger oral doses of the drug. With the amounts used in our study, we have not found this to be so.

Our findings support earlier reports, based on animal experimentation, that blood counts, blood pressure, and glomerular filtration rates remain unchanged with organomercurial therapy. Histological examination of organs of animals autopsied after prolonged administration of Neohydrin has revealed no differences in lung, heart, liver, or kidney between animals that had received Neohydrin over long periods and control animals.

Despite a growing number of reports indicating an absence of chronic mercurial toxicity in patients who have received mercurials over long periods, the feeling persists among some internists that large amounts of mercurials must be harmful to the kidneys and perhaps to other organs. In an attempt to answer this question we have examined the organs of 45 patients with congestive heart failure[3] to determine (1) whether mercury normally is present in the human body; (2) whether the administration of mercurials results in the accumulation of additional stores of mercury in the body; and (3) whether any damage results from the continued administration of organomercurials. Small quantities of mercury taken from the air and from food apparently result in harmless accumulations in the tissues of persons who have not been known to receive mercurial therapy. With organomercurial therapy, we find increased deposits of mercury in the kidney, the spleen, and the liver, but our investigations demonstrate clearly that neither small nor massive doses of organomercurials are harmful to kidney function, even when administered over long periods, except in the presence of oliguria or hyponatremia. Although damage to the renal tubules may occur if either of these conditions is present, the damage is only temporary and complete regeneration will occur once the electrolyte balance is restored.

Summary

In summary, our study demonstrates that (1) oral organomercurials effectively maintain an edema-free state in patients with congestive heart failure for 20 to 65 months; (2) in the absence of primary renal disease, elevated nonprotein nitrogen levels or moderate albuminuria do not contraindicate the administration of oral organomercurials; and (3) although mercurials are retained in the kidney tissue, their presence does not impair kidney function.

References

1. Cáceres, C. A. & J. C. Stauffer. 1955. Mercurialism; report of a case due to oral ingestion of a mercurial diuretic. New Engl. J. Med. **253:** 55–57.
2. Official Tests of the AMA Council on Pharmacy and Chemistry. 1953. J. Am. Med. Assoc. **152:** 331.
3. Griffith, G. C., E. M. Butt & J. Walker. 1954. The inorganic element content of certain human tissues. Ann. Internal Med. **41:** 501–509.

PROBLEMS OF MANAGEMENT OF CONGESTIVE HEART FAILURE, WITH SPECIAL REFERENCE TO THE REFRACTORY PATIENT

By Emanuel Goldberger
Columbia University, New York, N. Y.

Since this monograph is devoted to the action of the organomercurials, it is only natural that much of the clinical discussion should be related to problems of electrolyte balance and imbalance that may occur in the course of treatment of congestive heart failure.

I propose to deal particularly with the problems involved in the management of congestive heart failure, with special reference to the refractory patient, and I shall also discuss the question of electrolyte imbalance as it is related to mercurial therapy and to refractory failure. Before I do so, however, I should like to emphasize the fact that, even though a patient on mercurial therapy becomes refractory, this does *not* necessarily mean that the refractory state is due to the mercurials. For this reason I shall begin my presentation by describing, in rather general terms, some of the clinical conditions that may cause refractory heart failure or that may be associated with it.

For example, some of the more common conditions that can produce a refractory state of heart failure are:

(1) *Hypermetabolism from any cause.* In other words, any condition that can produce heart failure of its own accord and or that is associated with an increased cardiac output, such as:

(a) Hyperthyroidism.

(b) Peripheral arteriovenous fistula.

(c) Beriberi.

(d) Some cases of chronic pulmonary disease with pulmonary fibrosis and emphysema. Here the distortion of the pulmonary architecture causes the establishment of fistulous communications between the smaller pulmonary and bronchial arteries.

(e) Paget's disease, in which similar vascular fistulas develop in the affected bones.

(f) Some cases of cirrhosis of the liver.

(g) Severe anemias.

(h) Febrile states.

(2) *Small, multiple pulmonary infarcts.* These may be due to emboli either from the veins of the lower extremities or, more frequently, from the right atrial appendage of the heart, especially in cases of mitral stenosis. In this case, the febrile state also produces a strain on the heart. In addition, the disturbance of the pulmonary capillary bed may be so great over a period of time that a severe cor pulmonale may occur. Most of the cases of small pulmonary infarction are not recognized clinically, and the patient is usually treated for recurrent bouts of so-called pneumonia or pleurisy.

(3) *Cardiac conditions.* For example, the development of auricular fibrillation may be sufficient to produce a marked exacerbation of heart failure. The

development of a so-called silent myocardial infarct may be manifested merely by progressive, intractable failure, rather than by the usual clinical signs, such as pain and shock. Other less common causes of intractable heart failure due to myocardial disease, to mention a few, are constrictive pericarditis, specific types of myocarditis, and primary amyloidosis.

(4) *Digitalis intoxication.* I do not imply that digitalis by itself can cause refractory heart failure. However, when toxicity occurs, digitalis can cause nausea which, if prolonged, can lead to malnutrition or vomiting, which in turn can lead to a loss of electrolytes, particularly potassium, as well as to a loss of fluid. This may result in the very complex syndrome of peripheral edema associated with generalized dehydration. In addition, the so-called dilution syndrome, due to the retention of water, may result. I might also mention that any of these conditions may likewise cause the dilution syndrome.

(5) *Physiological changes produced by excessive use of diuretic agents.* Examples of these changes are the well-known phenomenon of hypochloremic alkalosis due to long-continued loss of chlorides in the urine or from the organomercurials, and the syndrome of hypochloremic acidosis due to a loss of both sodium and chloride, particularly in patients with renal disease.

(6) *Excessive loss of salt.* This factor, which may also cause refractory heart failure, is in many ways related to the use of diuretics, but it may exist as an independent factor. It may result from mechanical measures such as paracenteses and diarrhea or, more important, from a low salt intake.

My own observations seem to indicate that a low salt intake may occasionally lead to difficulties, especially in patients with severe congestive heart failure due to coronary artery disease. I should therefore like to describe briefly a case in which it is possible that stringent salt restriction may have been responsible, in part, for a complication that I have not seen previously described or emphasized; namely, the development of myocardial infarction.

The patient was a 66-year-old white female who, six years previously, had developed dyspnea, precordial pain, and edema, and had been given nitroglycerin and digitalis by a local doctor. She had done fairly well for 6 months under this treatment. Then, her symptoms having become worse, she entered a local hospital. There she had been given digitalis, a low-sodium diet, and mercurials, and had also received multiple chest taps because of persistent serosanguinous bilateral pleural effusions. In a period of 6 months, she had lost 40 pounds in weight. She was discharged and then, because of her generally poor condition, she was rehospitalized after 2 weeks.

Her weight on admission was 107¼ lb. She showed signs of severe right- and left-sided heart failure with bilateral pleural effusions. Because of X-ray findings of an enlarged left ventricle, electrocardiographic findings of left ventricular hypertrophy and strain and of a rough aortic systolic murmur, an etiological diagnosis of aortic stenosis was made. The cardiogram also showed RS-T signs of digitalis effects.

The patient was placed on a low-sodium diet containing 500 mg. sodium (equivalent to 1.25 gm. of salt) and on the following medications: (1) Digoxin, 0.25 mg. daily; (2) potassium triplex solution (Lilly), 15 c.c. (approximately

40 mEq.) daily; (3) ammonium chloride (25 per cent solution), 15 c.c. (65 mEq.) daily; and (4) 2 c.c. of mercaptomerin (Thiomerin) daily.

The day after her admission, the patient's weight was $106\frac{1}{4}$ lb., down 1 lb. A right thoracentesis was performed, and 1300 c.c. of serosanguinous fluid was removed.

Two days after admission, 850 c.c. more fluid was removed from the left chest. The patient's weight at this time was $104\frac{3}{4}$ lb., a loss of 3 lb. from the previous day.

Laboratory findings at this time were: serum sodium, 137 mEq.; potassium, 4.6 mEq.; CO_2, 32.1 mEq.; and chlorides, 92.2 mEq.

The next day, at 3 P.M., she stated that her mouth was dry. Examination showed that the skin of her abdomen had lost its tone. An infusion of glucose in distilled water was ordered.

One hour later, her pulmonary congestion was much more marked, and she was placed in an oxygen tent. Four hours later, at 8:30 P.M., she was in shock, with pulmonary congestion. She was treated with levarteronol bitartrate (Levophed), with improvement. However, by 10 P.M. she had gone into shock again, along with marked pulmonary congestion. Six hours later she died.

Autopsy disclosed a markedly calcified and stenotic aortic valve with pinpoint coronary ostia. The coronary arteries also showed severe arteriosclerotic changes, but there was no occlusion of the coronary artery. The myocardium showed extensive scarring over the left ventricle and a recent infarct near the apex.

What actually caused this woman to die?

The pathologically minded physician might state that she had an aortic stenosis, with involvement of the coronary ostia that produced coronary insufficiency. This condition was further complicated by severe coronary artery disease. Therefore, as a result of long-continued anoxia and coronary insufficiency, she developed myocardial infarction *without* coronary artery occlusion – a common occurrence in aortic stenosis—as a result of which she went into shock and died.

The physiologically minded clinician would point to the moderately low serum chloride and the moderately elevated CO_2 levels and state that this patient had a hypochloremic alkalosis due to excessive mercurials that was partially responsible for her death.

My own belief is that, in spite of a relatively normal serum sodium level of 137 mEq., this woman had salt depletion and dehydration. This decreased her circulating blood volume and her cardiac output, resulting in coronary insufficiency, shock, myocardial infarction, and death. In other words, it is probable that the myocardial infarction was the result, rather than the cause, of her shock. Of course, this cannot be proved.

I believe, however, that in selected cases of congestive heart failure due to coronary artery disease it might be possible to prevent such a complication of shock and myocardial infarction by liberalizing the salt intake. This raises a very important question. What is an optimum salt intake for a patient with congestive heart failure? I do not think that anyone can answer this question at the present time. Too much salt will aggravate the failure. Too little may embarrass the circulation.

In a pamphlet prepared by the American Heart Association,[1] low-salt diets are divided into 3 groups: (1) mild restriction, or 1.5 to 3 gm. sodium (3.75 to 7.5 gm. salt) per day; (2) moderate restriction, or 0.5 to 1.5 gm. sodium (1.25 to 3.75 gm. salt) per day; and (3) severe restriction, or less than 0.5 gm. sodium (less than 1.25 gm. salt) per day.

One can, if one wishes, choose any one of these diets and observe the patient carefully. What I have been doing recently, however, is attempting to place the salt intake of such patients on a more quantitative basis, using what I have called a natural salt diet. In order to do so I suggest that the patient be given a minimal low-sodium diet, namely, one containing less than 500 mg. sodium daily.[2]

It is necessary, next, to make certain that the fluid intake is adequate. We know that fluid restriction is not necessary. However, I consider it neither necessary nor desirable to force water on the patient, as has been advocated by Schemm and Hurst.[3]

A simple rule that I use is the following: the specific gravity of the urine should be determined in the morning, after the patient has gone without fluids for a 12-hour period (overnight). Sufficient fluids should be given to keep the specific gravity in the first morning specimen below this level. If the specific gravity is above 1.020, enough fluid should be given to bring it below this level. A daily intake of approximately 2000 c.c. of fluid is adequate. One quart of this fluid can consist of whole milk, which supplies about 500 mg. of sodium.

The patient should be allowed to add salt —pure salt—in definite quantities. This can be done very easily by using an ordinary No. 0 gelatin capsule. When this capsule is filled with salt it holds almost exactly 1 gm. (400 mg. sodium). This salt can be sprinkled on the food. This can be done very easily by puncturing an end of the capsule a few times with a pin, making the capsule a miniature salt shaker.

This procedure accomplishes 2 things. First, salt *on* the food makes it taste better than salt *in* the food. Second, and more important, the doctor can regulate, at will, the amount of salt the patient is using.

The diet described will contain the following amounts of sodium: 500 mg. in the basic diet, 500 mg. in the milk, and 400 mg. in the added salt, a total of 1.4 gm. sodium (equivalent to 3.5 gm. of salt). If symptoms of salt depletion, such as weakness and thirst, develop or continue, the salt intake can be increased in 0.5- to 1-gm. quantities. If the failure becomes aggravated, the quantity of salt can be similarly decreased.

Organomercurials should be used. I prefer to use oral administration whenever possible. For this purpose I use either chlormerodrin (Neohydrin) or mercumatilin (Cumertilin), which is about half as effective as Neohydrin. The daily dose is 1 to 6 tablets of either drug, given after breakfast. For subcutaneous or intramuscular use, either meralluride (Mercuhydrin) or Thiomerin is satisfactory. Minimal doses, 0.5 to 2 c.c., should be used.

Electrolyte depletion should be avoided. For this purpose I prescribe 6 gm. of ammonium chloride daily on 2 days of each week, either as uncoated tablets, capsules, or in a 25-per cent solution. In addition, from 3 to 9 gm. of potassium chloride, or a mixture of potassium salts, are prescribed daily for the remaining days of the week. I utilize the electrocardiogram roughly to determine the amount of potassium to be prescribed.

Finally, digitalis should be continued, but in small doses. By that I mean a daily maintenance dose, perhaps of Digoxin, which I use routinely, of 0.25 to 0.5 mg. Larger doses have not proved useful.

To conclude, then: the best treatment for refractory heart failure is, first, to find the cause of the condition, if possible. Second, to try, by energetic diuretic therapy, to prevent the fluid and electrolyte disturbances that occur so often. Thus the conscientious physician must pursue a wavering and stormy course between (1) the Scylla of undertreatment and persistence of severe failure and (2) the Charybdis of overtreatment and the development of serious fluid and electrolyte complications. This merely indicates that the last word on the treatment of heart failure is yet to be written.

References

1. American Heart Association. 1952. Food For Your Heart. New York, N. Y.
2. Goldberger, E. 1953. Heart Disease—Its Diagnosis and Treatment. 2nd ed. Lea & Febiger. Philadelphia, Pa.
3. Schemm, F. R. & W. W. Hurst. 1950. Water balance in heart and kidney disease as related to edema and oliguria. Med. Clin. N. Amer. **34:** 571.

MERCURIAL DIURETICS IN PRE-ECLAMPSIA AND OTHER CLINICAL INDICATIONS FOR THE USE OF MERCURIALS

By James W. Hendrick
Jacksonville, Fla.

Present-day obstetrics is confronted chiefly by 3 major problems: (1) hemorrhage, (2) infection, and (3) pre-eclampsia. The management of the first 2 of these, hemorrhage and infection, has been greatly improved in recent years by the use of blood transfusions and antibiotics. The third major obstetrical problem, pre-eclampsia and eclampsia, is the subject of this paper. This disease constitutes a threat to both mother and fetus, accounting in the United States for probably 1,000 maternal fatalities and possibly 30,000 fetal deaths each year. In the South the incidence of this disease approximates 18 per cent of all pregnancies. In addition, reports from Philadelphia[1] point out that eclampsia caused 10.8 per cent of the maternal deaths there in 1940 and that the percentage increased to 20.8 in 1950, although the total number of maternal deaths declined from 2.4 to 1 per thousand.

Pre-eclampsia is a specific disease of pregnancy, usually having its onset during the latter trimester and typically exhibiting a triad of findings: (1) hypertension, (2) edema, and (3) proteinuria. The earliest evidences of toxemia are an abnormal gain in weight and the appearance of edema, usually preceding the hypertension. Thorough prenatal care and early recognition and appropriate treatment of the symptoms of the oncoming toxemia present the best opportunity for halting the progression of pre-eclampsia to its convulsive phase, eclampsia.

Although the presenting symptoms of pre-eclampsia are evident, research has not uncovered the underlying etiology of the process. No specific cause is known. Of particular recent interest is research indicating that normal pregnancy presents a picture of a rising level of corticosteroids associated with an increased retention of sodium and water. This physiological trend becomes accentuated in pre-eclampsia, with the excretion of corticosteroids about 61 per cent higher than normal.[2] An increase in the sodium-retaining factor in toxemia has been reported;[3] this is probably due to aldosterone, the most vigorous sodium retainer of any steroid. Whether the conditions revealed by these findings are the cause or result of the pre-eclamptic process remains to be seen. Another theory postulates the impairment of circulation to the uterus and placenta, with an absorption of toxic substances into the maternal circulation that results in toxemia. Perhaps there may be a number of specific factors such as dietary deficiency, infection, placental degeneration, fatigue, emotional stress, placental separation, and excessive salt intake. We must also recognize certain predisposing factors such as first pregnancy, previous toxemia or hypertension, diabetes, the conception of twins or a large baby, and polyhydramnios.

Thus, in pre-eclampsia, in the absence of a known specific etiology, therapy must be directed toward the symptoms present. Since rapid gain in weight, edema, and hypertension are the earliest of these symptoms, usual prenatal care has consisted of low salt intake and sedation. In 1950, noting the effective use by the medical services of mercurial diuretics for the mobilization of sodium and water in cardiac disease, a group of co-workers and I at Charity Hospital in New Orleans, La., considered the use of mercurial diuretics in toxemic edema.[4] Literature at that time revealed that Brown and Bradbury[5] in 1948 had compared the effects of various drugs in promoting the elimination of excess sodium and fluid in pregnant women; in their series, they had reached the conclusion that mercurial diuretics were most effective. Other workers had also investigated mercurial usage in toxemic edema.[6-8] Therefore, based on the premise that the abnormal retention of sodium and water is a fundamental disorder in pre-eclampsia and that mercurials are effective in eliminating sodium and water, a study of 100 cases was undertaken.[9]

Methods and Results

In this study the selection of patients to be treated was made on the basis of excessive weight gain and the development of pitting edema. These obvious indications must be stressed, for deviation from these criteria results in a poor response. The patients were admitted to the toxemia ward of Charity Hospital, where a base-line weight and urinary output was immediately recorded and a thorough workup was undertaken. After the controlled base lines were obtained, the dosage usually instituted was 2 c.c. of mercurial diuretics administered intramuscularly; this dosage was occasionally repeated in 48 hours. No toxic effects were noted in this series of cases. In the presence of a good diuretic response and an adequate fluid intake we have seen no harmful effects in using mercurials in toxemia of pregnancy, nor have we observed elevated blood-urea nitrogen values. No fetal harm has been noted. Amniotic fluid obtained prior to delivery in 2 patients has shown no trace of mercury. Evaluation of therapy has been made on the basis of increased urinary output and the loss of weight. These analyses revealed good results in 75 patients, fair results in 7, and poor results in 10. The cases in which toxemia did not respond well were invariably those without pitting edema. Eight patients delivered so soon after treatment that they could not be evaluated. The average loss of weight in the 75 patients with whom good results were obtained was 6.7 lb.

Mercurials have been used in our study with excellent results in severe toxemics with poor urinary output. One case is that of a 32-year-old Para IV admitted at 7 months' gestation with a severe abruptio placentae, 4-plus albumin, no fetal heart tones, and shock. A Porro cesarean section was done, obtaining stillborn twins. On the first postoperative day the urinary output was 27 c.c. with a fluid intake of 3750 c.c. On the next day her output was 260 c.c. The following day she was given 1 c.c. of mercurial intramuscularly; in the subsequent 24 hours her output was 3015 c.c. and she continued to have a satisfactory output and clinical course. A second case concerns a 20-year-old primigravida admitted at 7 months' gestation with hypertension 160/90, 4-plus albumin, and 2-plus pitting edema. Fetal heart tones were present, but the cervix was long and closed. She was placed on a toxemia routine, including sedation and intravenous glucose. Sixteen hours after admission, however, her total output had been only 45 c.c., and she was given 2 c.c. of mercurial intramuscularly. In the first hour after injection there was no output, but in the next hour there was 100 c.c. and, following this, a 744 c.c. output in the next 2 hours. The output remained adequate. Labor occurred 4 days later, a stillborn infant being delivered.

Flame-photometer determinations were made on serum and urine sodium and potassium in 39 normal pregnancies and 29 pre-eclamptics. It was found that serum sodium levels were the same in normal and toxic pregnancies, but that both were somewhat lower than nonpregnant levels. The most interesting results were obtained from urinary studies in pre-eclamptics showing a pronounced disposition toward the retention of sodium, a tendency even greater than in normal pregnancies. The normal nonpregnant value of sodium in grams per 24-hour urine specimen proved to be 4 to 5, but this figure was reduced in normal pregnancies to 3.1 and was further lowered to 2.36 in pre-eclamptics, thus demonstrating a marked tendency toward the retention of sodium. Further studies were made on 24 of the pre-eclamptic patients after the injection of 2 c.c. of mercurial diuretics administered intramuscularly; serum and urine were collected for the 24-hour period prior and subsequent to the injection. These studies have shown a marked increase in urinary sodium after mercurial injection, averaging 168.5 per cent more sodium than in the premercurial specimen.

Once we had observed the value of intramuscular mercurial therapy in the treatment of hospitalized toxemic patients, the next logical step was to consider the use of mercurials in prenatal care for the prevention of the more severe stages of pre-eclampsia and eclampsia. It was recognized that it would be desirable to have available a convenient effective oral diuretic that could be used on an outpatient basis and perhaps throughout the last trimester of pregnancy to prevent the accumulation of fluid and sodium. The introduction of a safe yet potent orally effective organomercurial diuretic, Neohydrin, seemed to offer promise in this problem. The New Orleans group therefore selected 52 patients with toxemia of pregnancy for a study utilizing Neohydrin.[10] Thirty-one of these patients were studied on an outpatient basis after being diagnosed as mild pre-eclamptics, and a base line was obtained by the usual regimen, including diet restriction, sedation, and rest. If no response was noted as indicated by increases in weight, blood pressure, or edema, Neohydrin was administered. The initial dosage commonly consisted of 8 tablets daily for 1 week, with a maintenance dosage of 4 to 6 tablets daily. The average duration of treatment was 2 weeks. Also, 21 patients exhibiting severe pre-eclampsia were hospitalized and given the routine toxemia therapy, including complete clinical and laboratory study, bed rest, recorded intake and output, and low-sodium diet. In the absence of clinical improvement within 4 days, the patient was treated with Neohydrin on a schedule similar to that for the ambulatory group.

Results

Results in this series were based on a lessening of edema and albuminuria, loss of weight and reduction of hypertension, and increased urinary output. Edema was effectively reduced in all cases, usually during the first 5 days of therapy, and more promptly in the hospitalized group. Of the 19 women who had albuminuria from 1 to 4 plus, 5 cases showed a disappearance of albumin from the urine. The average patient's weight prior to therapy was 182.8 lb. and 176 following treatment. The average systolic blood pressure was 151 mm. mercury prior to, and 124.8 following, treatment. In the entire group there was general improvement characterized by loss of weight, loss of edema, reduced albuminuria, and lowered blood pressure. The 21 hospitalized patients with severe pre-eclampsia were also given a complete clinical and laboratory workup and 4 days of routine therapy for a control period. If no apparent improvement occurred in this time, oral Neohydrin was instituted. Weight loss in this group amounted to as much as 13 lb. in 1 week in 1 patient; in others it amounted to as much as 5 to 30 lb. in 2 weeks, 5 to 10 lb. in 3 weeks, and 9 to 25 lb. in 4 weeks. One patient lost 19 lb. in 6 weeks. The average urinary output per 24-hour period was increased from 2200 c.c. prior to treatment to an average output for each of the first 5 days of 3600 c.c., 4000 c.c., 3700 c.c., 3500 c.c., and 3500 c.c., respectively. Electrolyte studies in this group also revealed an increase in sodium excretion in the urine averaging 80 per cent. Two cases are briefly presented below to illustrate the impressive responses to Neohydrin and the excellent control of severe pre-eclamptic toxemia.

The first case was a 24-year-old colored female Para II who was first seen at 7½-months' gestation with 4-plus edema, 4-plus albuminuria, headache, and a blood pressure of 164/96. After 4 days of conservative therapy including sedation and complete bed rest, without improvement, Neohydrin therapy was instituted in a dosage of 80 mg. daily (2 tablets 4 times daily). From a pretreatment urinary output of 1500 c.c. per 24 hours, the output rose to 3000 c.c. per 24 hours, and then to 7000 c.c. the second 24 hours. By the sixth day this amount was gradually reduced to 3500 c.c. and remained at that level. The urinary sodium loss rose from only 0.5 gm. per 24 hours before treatment to 7.2 gm. for the second day, and it continued above normal until the eighth day. On the fifth day the patient's blood pressure was 120/90 and, after 15 days, it was 140/96, at which time she had lost 30 lb. and no longer showed any indication of albuminuria. She went into spontaneous labor, delivered normal live male premature twins uneventfully, and had a normal postpartum period.

Another case was that of a 20-year-old primigravida admitted 6 weeks from term, with twins, a blood pressure of 180/120, 4-plus albuminuria, and 4-plus edema. This patient was treated in accordance with the usual toxemia routine until a basal condition was established, at which time she was put on Neohydrin (2 tablets every 6 hours). The urinary output of 1500 c.c. per 24 hours before treatment rose to 5000 c.c. during the 24 hours following treatment, then to 6000 and 8000 c.c., respectively, for 2 more days. The edema disappeared, the blood pressure fell to 130/90, the albumin decreased to 2 plus, and the weight declined from 145 to 116 lb. The patient was maintained on Neohydrin (1 tablet twice a day) and approximately 3 weeks later, she delivered normal viable twins.

On the basis of our experiences we conclude that mercurial diuretics are a valuable adjunct to therapy in cases of pre-eclampsia with sudden gain in weight and pitting edema. By increasing the urinary output of sodium and water, mercurials have been shown to eliminate edema, to cause a reduction in weight, blood pressure, and albuminuria, and to contribute valuably to the clinical management of ambulatory and hospitalized toxemic patients. An oral mercurial, Neohydrin, has proved particularly effective in this management and has lent itself well to early prenatal ambulatory and outpatient cases, which is of considerable value in the prevention of severe pre-eclampsia.

Premenstrual Tension Syndrome and Therapy

The premenstrual tension syndrome is a symptom-complex that makes a cyclic appearance during the week to 10 days preceding menstrual flow, disappearing with the onset of menses. The most common symptoms are bloating, backache, painful swollen breasts, a gain in weight with or without visible edema of the ankles and face, a general malaise, "loginess," headache, anxiety, depression, and irritability. This tension syndrome, seen frequently in clinical practice, occurs to a pathological degree sufficient to require therapy in about 20 per cent of women. The importance of these symptoms must not be underestimated, for even though they are seldom incapacitating, the family, business, and social relations of the affected female are greatly disturbed at this time. Domestic tragedies, unpremeditated criminal acts, and industrial inefficiency may be attributed to a great extent to premenstrual tension. Though disagreement exists as to the basic etiology of premenstrual tension, most workers agree that the major symptoms are due to the retention of water. The most objective finding is a premenstrual gain of water weight from 4 to 12 lb., often with visible edema of the tissues. Frank[11] described the complex in 1931, and he ascribed it to an abnormally high amount of estrogen. Greenhill and Freed[12] contended that the premenstrual distress is the result of the retention of sodium under the influence of ovarian steroids, and they ascribed the symptoms as arising from the specific organ (the brain, the intestine, or the nervous system) affected by the edema. Greene and Dalton[13] and others[14] attributed the symptoms to an abnormally high estradiol-progesterone ratio. Thorn and his co-workers[15] attributed the retention of water to ovarian steroids, while Bickers[16] emphasized the high urine and blood titers of the antidiuretic factor of the posterior pituitary.

Therapy

Although there are a multitude of theories, the common denominator in all appears to be the premenstrual retention of sodium and water. Thus the therapy has been directed toward this abnormality. Progesterone has been used by some[17-20] to correct the supposed high estrogen-progesterone ratio. Testosterone has been used in an effort to modify the premenstrual ovarian steroids. A low-sodium diet for the last 2 weeks of the menstrual cycle is a widely accepted aid to therapy. Some practitioners have employed sedatives, including the recently introduced tranquilizing drugs. Antihistiminics, stimulants, and vitamin-B complex have also been employed. The most common basis of treatment is a diuretic. The use of ammonium chloride has been described, as has the use of oral theophylline diuretics and of Diamox. The administration of mercurial diuretics, generally considered to be the most efficient mobilizers of sodium and water, appears to be the most direct mode of therapy. Jacobsen[19] employs mercurial diuretics, low-sodium diet, and progesterone in the premenstrual week of his severest cases. Greenhill,[21] though most commonly employing ammonium chloride, considers mercurial injection effective for relief at the height of premenstrual tension. In my experience, the use of Neohydrin has proved most effective for specific therapy, for it has the particular advantage of being an effective oral mercurial diuretic and of affording relief in a dosage of 1 or 2 tablets daily for 5 to 7 days premenstrually.

Other Clinical Usages of Mercurials

Certain other disease syndromes associated with fluid and electrolyte accumulation have been managed in part by mercurial therapy. Migraine headache is one such syndrome; its pathological physiology is probably a neurovascular mechanism with an electrolyte and fluid imbalance. Interestingly enough, its onset is often associated with premenstrual tension. The probable value of an effective diuretic is obvious, and several investigators using such therapy have reported excellent results.[22] An oral mercurial appears particularly adaptable to outpatient control.

Menière's syndrome has also been postulated to be an allergic reaction with secondary edema of the labyrinth of the ear. Several investigators[23, 24] have demonstrated the value of management by a low-sodium diet and the administration of diuretics to produce efficient dehydration.

The ascites in cirrhosis of the liver probably results from elevated portal venous pressure and a lowered serum albumin level; however, sodium and fluid are retained in the body in this condition, and dietary sodium restriction is a helpful control. Further efficient reduction in ascites, often diminishing the need for paracenteses, has been produced by means of mercurial diuretics.[25] The edema of the nephrotic syndrome has also responded favorably, with no toxic results,[26] to Mercuhydrin.

Another fluid-accumulation syndrome that I have seen benefited by mercurials is polyhydramnios, which is the accumulation during pregnancy of excessive amounts of amniotic fluid. Hussar and Hoiley,[27] have treated bromide intoxications with diuretics by a combination of ammonium chloride and mercurial diuretics. The aim in therapy in this condition is to promote a quick elimination of the bromide ion from the body. These investigators suggest that mercurials block tubular reabsorption of the bromide ion, and they report excellent clinical results.

Craig[28] reports that the dietary management of obesity has been aided by Mercuhydrin and Neohydrin, eliminating the latent period of constant weight so often seen at the beginning of low caloric treatment. He feels that administration of Mercuhydrin during the first 3 days of treatment, followed by 3 tablets of Neohydrin daily for another 10 days, effectively drains the obese tissues of occult edema.

Pain in intractable angina pectoris, refractory to usual routine methods of treatment, has been reported to respond favorably to mercurial diuretic therapy. Both Gilbert[29] and Paul,[30] in separate reports, have described the pain relief resulting from the diuresis and loss of weight following Mercuhydrin therapy, even though visible edema was not present.

Gelfand and Widlitz[31] have employed Mercuhydrin as an aid in differentiating cardiac from bronchial asthma. The basis for this differentiation is that the dyspnea, cough, and bronchospasm in cardiac asthma responds favorably to an injection of Mercuhydrin whereas, in true allergic asthma, this picture is unchanged. The therapeutic value of Mercuhydrin in cardiac asthma has been emphasized elsewhere.[32]

References

1. Carrington, E. R. & J. Willson. 1953. Am. J. Obstet. Gynecol. **65:** 12.
2. Venning, E. H., B. Singer & S. A. Simpson. 1954. Am. J. Obstet. Gynecol. **67:** 542.
3. Barnes, A. C. & E. J. Quilligan. 1956. Am. J. Obstet. Gynecol. **71:** 670.
4. Smith, R. C., H. K. Miller & J. W. Hendrick. 1951. New Orleans Med. Surg. J. **104:** 144.
5. Brown, W. E. &. J. T. Bradbury. 1948. Am. J. Obstet. Gynecol. **56:** 1.
6. Brown, W. E. & C. G. Sutherland. 1953. GP. **8:** 65.
7. deAlvarez, R. R. & W. F. Gabrio. 1953. Am. J. Obstet. Gynecol. **65:** 833.
8. deAlvarez, R. R. & D. F. Richards. 1952. Am. J. Obstet. Gynecol. **63:** 1263.
9. Hendrick, J. W. 1954. Bull. Tulane Univ. Med. Faculty. **13:** 169.
10. Dyer, I., J. W. Hendrick, R. Lapointe & J. W. Sewell. 1955. In press.
11. Frank, R. T. 1931. Arch. Neurol. Psychiat. **26:** 1053.
12. Greenhill, J. P. & S. C. Freed. 1940. Endocrinology. **26:** 529.
13. Greene, R. & K. Dalton. 1953. Brit Med. J. **1:** 4818.
14. Morton, J. H. 1950. Am. J. Obstet. Gynecol. **60:** 343.
15. Thorn, G. W., K. R. Nelson & D. W. Thorn. 1938. Endocrinology. **22:** 155.
16. Bickers, W. 1950. New Engl. J. Med. **243:** 645.
17. Dalton, K. 1954. Brit. Med. J. **2:** 1071.
18. Israel, S. L. 1938. J. Am. Med. Assoc. **110:** 172.
19. Jacobsen, V. C. 1955. N. Y. State J. Med. : 1613.
20. Mukherjee, C. 1954. J. Indian Med. Assoc. **24:** 81.
21. Greenhill, J. P. 1955–1956. Year Book Obstet. Gynecol. : 502.
22. Foldes, E. 1952. N. Y. State J. Med. **52:** 1307.
23. Dintenfass, A. 1950. Arch. Otolaryngol. **51:** 582.
24. Foldes, E. 1954. N. Y. State J. Med. **54:** 1377.
25. Atkinson, M., A. Paton & S. Sherlock. 1954. Lancet. : 128.
26. Finkelstein, M. B. & C. J. Smyth. 1945. J. Mich. State Med. Soc. **45:** 1618.
27. Hussar, A. E. & H. L. Holley. 1956. Am. J. Med. **1:** 100.
28. Craig, P. E. 1955. Medical Times. **83:** 156.
29. Gilbert, N. S. 1950. Dade County (Fla.) Med. Assoc. Bull. **1.**
30. Paul, O. 1951. Med. Clin. N. Amer. **35:** 63.
31. Gelfand, M. L. & A. R. Widlitz. 1951. Am. J. Med. Sci. **221:** 250.
32. Gelfand, M. 1953. Intern. Record of Med. **166:** 420.

DISCUSSION: PART III

Harry Gold, *Chairman*

Cornell University Medical College, New York, N. Y.

John Moyer (*Baylor University College of Medicine, Houston, Texas*): In an original report given in 1952[1] on the use of chlormerodrin (Neohydrin), our response rate was 90 per cent in outpatient use; that is, 90 per cent of the patients with heart failure were controlled just as well with 6 tablets of Neohydrin given daily in divided doses by the oral route as they were with 2 c.c. of meralluride sodium solution (Mercuhydrin) given parenterally 3 times a week. Now, after 4 years of follow-up, we still obtain a response rate that is nearly identical with that of 89.5 per cent just reported by Evans. This indicates that the drug is just as effective in long-term use as the short-term studies suggested.

One frequently overlooked fact about intractable heart failure is that it is usually evidence of a deteriorating cardiac disease. Heart failure is a progressive disease in which, finally, there comes a time when the patient will not respond to any therapy, no matter how hard the therapist looks for alterations in the plasma concentration of sodium, chloride, and other electrolytes as being responsible for the condition. Depleted serum electrolytes usually indicate a deteriorated cardiovascular status, and the prognosis is usually unfavorable even if the serum electrolytes are corrected by such measures as the administration of 5 per cent sodium chloride.

I should also like to discuss the difference in the acute dosage-response curve between acetazoleamide (Diamox) and Neohydrin. The maximum diuresis after the administration of Diamox is achieved at a dose of about 125 to 250 mg. Higher doses, up to 2 gm. (8 tablets) a day, can be given without producing an additional diuresis, as shown in FIGURE 1. Therefore one cannot keep increasing the dose of Diamox in the patient with moderate to severe heart failure and expect an increasingly effective diuresis to follow.

On the contrary, when the dose of Neohydrin is increased above the 60 mg. Hg equivalent dose, an increasingly greater diuretic response is observed (FIGURES 1 and 2). This suggests that, in the patient with mild heart failure, both Diamox and Neohydrin are adequate, insofar as loss of weight is concerned, when these drugs can be given intermittently. However, when maximum diuresis is desired in the patient with severe heart failure, Diamox is of limited value, and Neohydrin is by far the superior oral diuretic.

The dosage-response curves obtained from studies on Mercuhydrin, Diamox, Neohydrin, and Mersoben confirm the previous observations of Greiner and Gold[4] that Mercuhydrin produces a dosage-response curve showing a geometric progression between doses of 0.5 and 2 c.c., which are equivalent to 20 to 80 mg. Hg. Increasing the dose above this level produces very little additional diuresis. Mersoben and Mercuhydrin follow a similar and parallel dosage-response curve, but Mersoben appears to be more potent than Mercuhydrin.

When Mersoben, given parenterally, is compared with Neohydrin, given

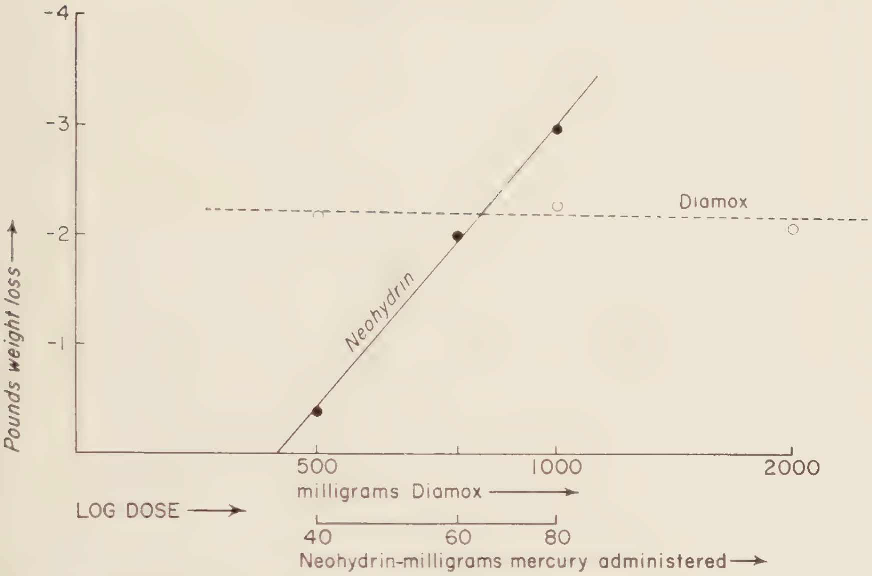


FIGURE 1. Dosage response of patients to Diamox, as compared to their response to Neohydrin. (Reproduced by permission from the *Journal of Chronic Diseases*.[2])

orally (FIGURE 2), the curves obtained are not parallel, but both show linear responses. Mersoben is effective at a much smaller dose equivalent of mercury than is Neohydrin. This is doubtless due to the method of administration and relatively poor absorption of Neohydrin from the intestinal tract, as com-

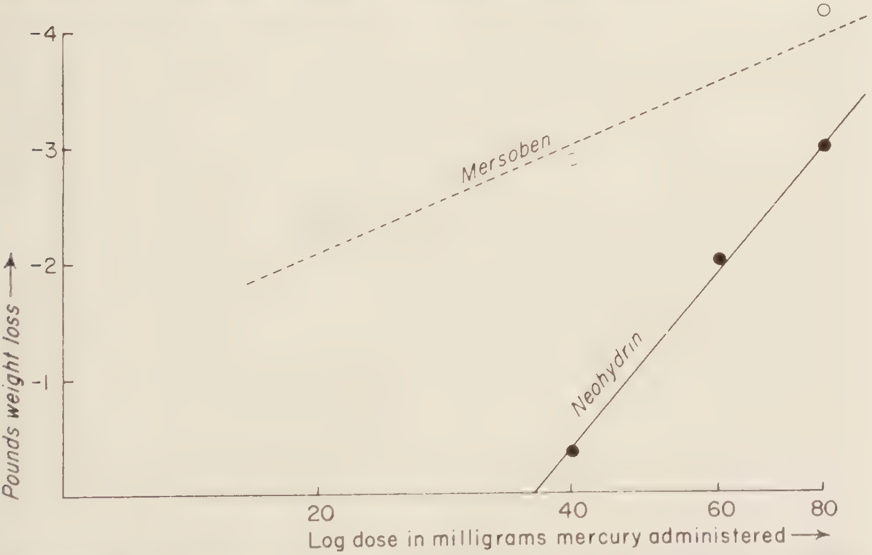


FIGURE 2. Comparison of Mersoben administered parenterally and Neohydrin administered orally. (Reproduced by permission from the *Journal of Chronic Diseases*.[3])

pared to the absorption of Mersoben, which was given parenterally. It is thus necessary to administer a relatively large amount of Neohydrin before a sufficient amount of it is delivered to the kidneys to reach the diuretic threshold in the renal tubules. However, as the diuretic threshold is exceeded, the dosage-response curve of Neohydrin rises very rapidly, so that the diuretic response to 1 c.c. of Mersoben (equivalent to 40 mg. Hg) is practically the same as to 8 tablets of Neohydrin (equivalent to 80 mg. Hg). In these doses, Neohydrin given orally will produce a degree of diuresis equivalent to that produced by Mersoben given parenterally.

References

1. Moyer, J. H., C. A. Handley & I. Wilford. 1952. Results over a two-year period on three experimental diuretics administered orally to patients with cardiac failure. Am. Heart J. **44:** 608–614.
2. Moyer, J. H. & W. Hughes. 1955. A comparative study of Neohydrin and Diamox alone and in combination for the treatment of severe congestive heart failure. J. Chronic Diseases. **2:** 678–686.
3. Moyer, J. H., R. G. McConn, R. A. Seibert, E. W. Dennis & W. Hughes. 1955. A comparative study of Mersoben, Mercuhydrin (parenteral diuretics), Neohydrin, and Diamox (oral diuretics). J. Chronic Diseases. **2:** 670–677.
4. Greiner, T. & H. Gold. 1951. Bioassay of diuretic agents in patients with congestive heart failure. J. Pharmacol. Exptl. Therap. **103:** 431.

Theodore Greiner (*Cornell University Medical College, New York, N. Y.*): We have found that one half a tablet of Diamox is just as effective as 8 or 12 tablets. There is a sharp ceiling, a maximum response at about the same level of diuresis as that produced by 0.5 c.c. of any common mercurial diuretic injected into the muscle. A similar limited potency has been found with several other diuretic compounds that act by carbonic anhydrase inhibition.

T. H. Maren (*University of Florida, Gainesville, Fla.*): With respect to the dosage-response curve of Diamox, I think the physiological basis for it is the fact that at the usual clinical dose of 3 to 5 mg. kg. there is complete inhibition of renal carbonic anhydrase, so that increasing the dose or giving a more potent inhibitor cannot produce any further effect.

I should like to discuss the references made to homeostasis and sodium output. Some studies[1] were made at the Stamford Research Laboratories of the American Cyanamid Company, Stamford, Conn., on the effects of mercurial diuretics and carbonic anhydrase inhibitors on normal dogs.

On the first day following the injection of Mercuhydrin into a normal animal, there was a good output of sodium and chloride, with somewhat more chloride than sodium appearing in the urine. On the second and third days, however, the output was less than normal. Thus, this normal dog, following initial sodium chloride loss, was refractory to the further administration of a mercurial diuretic. By the fourth day, there was slight metabolic alkalosis. When Diamox was given, a strong bicarbonate diuresis resulted but practically no sodium was excreted, probably due to prior sodium loss. The bicarbonate ion was matched by potassium. Again, this shows that when a normal animal is depleted of an ion, it will not respond to a diuretic drug by excretion of this ion. Please note that I am not talking about disease, but about the normal individual or the normal dog.

I don't think there is any fundamental difference between the renal tolerance to a mercurial diuretic and the tolerance to a carbonic anhydrase inhibitor. The action of the former seems to be based on Na^+ or Cl^- loss, and of the latter on a systemic acidosis.

A very useful way to use these two drugs together is illustrated by another experiment. On the first day we gave Diamox to produce a good sodium diuresis with bicarbonate and, on the second day, we administered Mercuhydrin. Since the animal was acidotic due to loss of bicarbonate at this point, there was good response in terms of the loss of sodium and chloride, a response somewhat better than one would obtain with mercurials alone.

When we administered the organomercurial alone, the chloride output averaged 40 mEq. In the animal that we pretreated with Diamox, the output averaged 60 mEq.; in this acidotic setting, the effect of the mercurial was augmented. We found that no other combination was as effective in eliminating sodium in a 48-hour period.

Reference

1. Maren, T. H. 1955. Federation Proc. **14:** 366.

John Moyer: The mean weight response during therapy with the combination of Neohydrin and Diamox is similar to that obtained with Neohydrin alone. However, the combination of Neohydrin and Diamox appears to be more effective than Neohydrin alone in patients with severe congestive heart failure.

The differences in therapeutic effectiveness between these drugs are not as apparent when a single-dose response curve is used for evaluating these agents since, on a single-dose basis, 250 mg. of Diamox appears to be nearly as effective as 6 to 8 tablets (equivalent to 60 to 80 mg. Hg) of Neohydrin. However, when continuous diuresis is mandatory to control heart failure, Neohydrin proves its superiority even more clearly, since it continues to produce diuresis when administered daily. Diamox, on the contrary, is effective only when the heart failure is so mild that interrupted administration is feasible; for example, giving the drug 2 days per week, the procedure that we followed in the past when we determined the acute dosage-response to these agents. When more frequent diuretic effect or continuous diuresis is required, Diamox is inadequate, due to the apparent development of tolerance when this drug is administered too frequently.

I should like to comment on the references made to a dose of Neohydrin of 1 or 2 tablets a day. I doubt the therapeutic value of such a small dose, even in patients with minimal heart failure. I believe that 1 or 2 tablets a day is an ineffective dose or, more correctly, that it is a subthreshold therapeutic dose. We have done studies on the urinary excretion rate of Neohydrin following oral administration, and have found that the maximum absorption is 15 per cent, with an average of 8 to 12 per cent,[1] as reflected in mercury excretion via the kidneys. This means that if you gave a dose of 1 to 2 tablets a day, which would provide the equivalent of 10 to 20 mg. of mercury as Neohydrin, you would be depending on an equivalent of 1 to 3 mg. of mercury delivered to the kidney for the production of diuresis. I do not believe that this amount of the drug will produce diuresis, since we found that after parenteral administration of Neohydrin, a minimum of 8 to 10 mg. equivalent of mercury was required before diuresis or natriuresis could be demonstrated.[2]

We have additional evidence to prove this. Recently my colleagues, Ralph Ford and Charles Spurr, and I have been working on a bioassay technique that involves controlled metabolic studies. We find that a dosage of 4 tablets a day, given in divided doses, is the threshold at which we can statistically demonstrate diuresis as far as sodium, water, and chloride excretions are concerned; certainly diuresis cannot be demonstrated with a dose of less than 3 tablets a day.

In routine care of patients in heart failure, about 6 tablets a day are used in our clinic. We find that if we can control patients on less than 3 tablets a day, these same patients can be controlled equally well with a placebo. The results of such a study are summarized in FIGURE 1.

A final point to be emphasized concerns the low-salt syndrome and the problem of intractable heart failure. We should bear in mind that weakness and fatigue are symptoms of heart failure as well as of hyponatremia. I think this is why the diagnosis of low-salt syndrome made in the clinic so often fails to be supported when the serum levels of sodium are determined. In our outpatient cardiac clinic, we have seen very few cases—perhaps 5 or 6 a year—of the true low-salt syndrome. We frequently see the clinical signs but, when we determine the plasma sodium concentration, it is usually normal. Furthermore, when a state of true sodium depletion is found, it usually indicates a patient whose cardiovascular status is deteriorating, rather than a result of overtreatment.

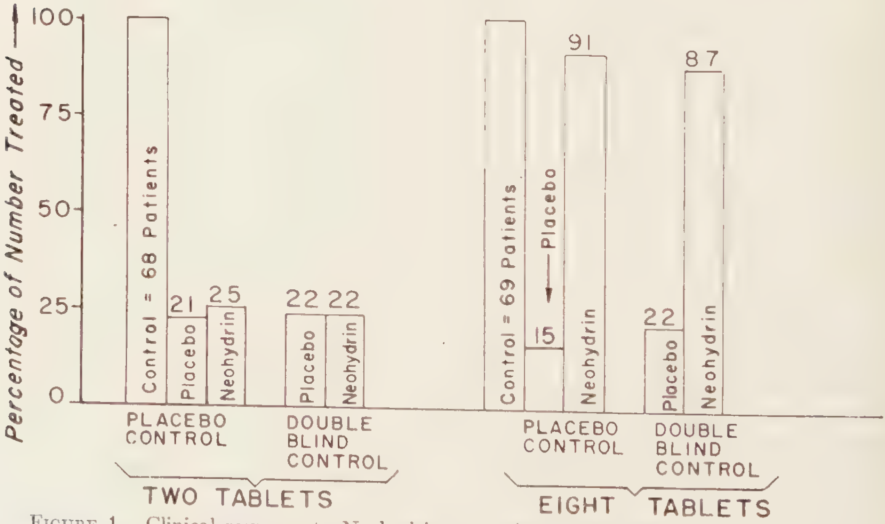


FIGURE 1. Clinical response to Neohydrin on patients with heart failure. Shown is a comparison of placebo control with the double blind technique. (Reproduced by permission from the *Archives of Internal Medicine*. 1956. Vol. 96, pp. 608–618.)

References

1. Moyer, J. H., C. A. Handley, R. A. Seibert & H. B. Snyder. 1953. Electrolyte, water, and mercury excretion after oral administration of Neohydrin. Arch. Internal Med. **92:** 847–855.
2. Moyer, J. H., C. A. Handley, R. A. Seibert, S. Mitchell & D. Papandrianos. 1952. Clinical diuretic studies on three new mercurial compounds. Am. Heart J. **44:** 281–293.

Theodore Greiner: I agree that 1 or 2 tablets of Neohydrin have little clinical effect and that about 4 tablets are required before a clinical response is apparent. However, with a sensitive measuring system the slight effects of small doses can be detected. There does not seem to be a sharp threshold dose, but rather a characteristic dosage-response relationship. On the basis of the chemical measurements presented here by Moyer, 15 per cent is the maximum absorption of Neohydrin when given by mouth. In clinical bioassay we found that the oral dose must be 4 times the intramuscular dose to produce the same diuretic effect. These results are close enough to suggest that clinical and chemical measurements confirm each other.

There is no doubt that oral mercurial diuretics have been useful tools in the management of congestive failure but we should not, in our enthusiasm, overlook the possibility of self-injection. Several patients in our clinics have given themselves injections of mercaptomerin (Thiomerin) for 4 years. Not many clinic patients want to try self-injection, but in these few it is a satisfactory solution to a difficult problem.

Gerson Lesser (*Goldwater Memorial Hospital, New York, N. Y.*): We have studied urinary electrolyte excretion in 1- or 2-hour fractions following the administration of Neohydrin. In those patients who retain sodium strongly, that is, who excrete less than 10 mEq. per day, we have never observed any significant change in electrolyte excretion with a single dose under 3 tablets.

In most of the studies presented in this monograph, however, the subjects do not fall into this category; most of them were excreting more than 20 mEq. of sodium per day. In such patients it is conceivable that a dose of 1 to 3 tablets might cause increased sodium excretion over a 6- to 8-hour period, but that "reactive compensation" might take place over the next 16- to 18-hour period. In such an instance, a 24-hour urine collection would not indicate any net increase in sodium excretion. We have studied only a few patients of this type, but in several of them the phenomenon of compensation was observed.

Therefore it probably cannot be stated conclusively at this time that a 1- or 2-tablet dose (10 to 20 mg. Hg) will not cause diuresis. From a therapeutic standpoint, however, 3 tablets a day would appear to represent a minimal effective dose.

Jacob Grossman (*Montefiore Hospital, New York, N. Y.*): I think that the danger of hyponatremia resulting from the severe restriction of salt has been somewhat overstated by Emanuel Goldberger. Once the patients have been made relatively "dry" following the introduction of salt restriction, what is there to cause the further excretion of sodium? These patients are seldom in negative sodium balance, so that the maintenance of a low salt diet will not of itself cause any continued or persistent salt depletion.

The use of mercurials in a patient who is also on salt restriction might favor the development of salt depletion. Even there, it might have been emphasized a little more that the urine lost under treatment with the mercurial alone is isotonic with respect to sodium and, on the basis of the sodium and water loss due to this therapy, one would not expect hyponatremia to develop. For this condition to occur, it is essential to have water retention superimposed on the conditions of dietary restriction and mercurial administration. The mechanism of this retention of water is what we must examine.

In reference to oral mercurial diuretics, although my own experience with them has been limited, I cannot help being impressed, on reading the reports of others, by the lack of certain very pertinent information.

We are told that when patients are III-plus or IV-plus heart failures, they require parenteral mercurials and must be brought down to grade I or II before an oral mercurial can be given. By that time, we find that, if we follow their weight on oral mercurials, they manage to hold it. Usually there is little mention of any restriction of sodium that may have been instituted at the same time.

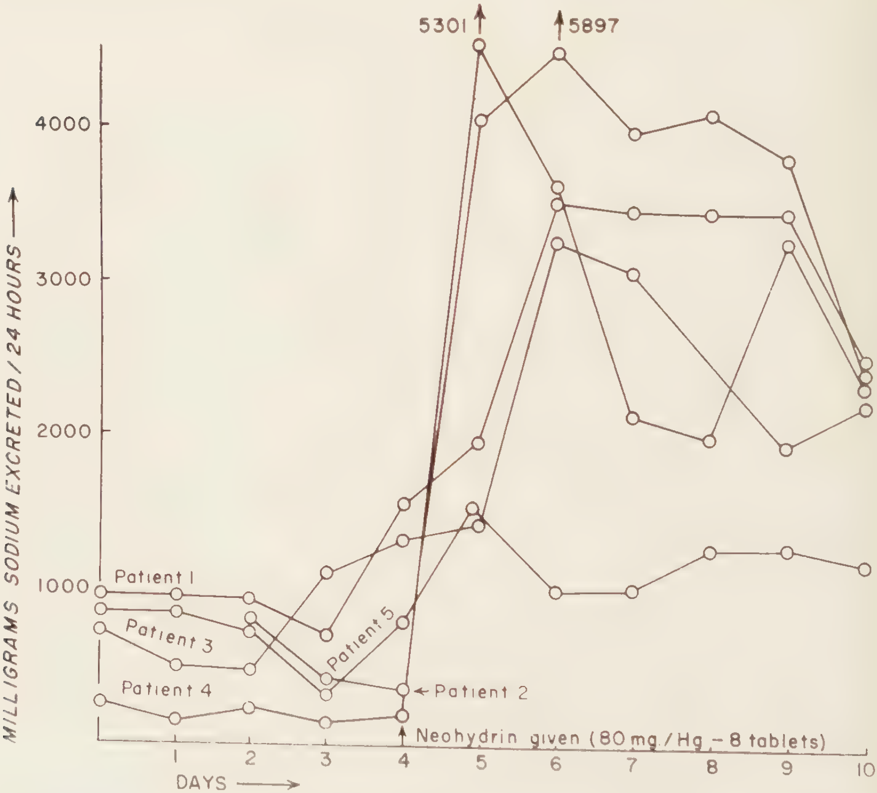


FIGURE 1. The effect of Neohydrin, administered orally, on the excretion of sodium over a 24 hour period. After 4 control days, Neohydrin was administered, after which there was a sharp increase in the excretion of sodium. (Reproduced by permission from the *Archives of Internal Medicine*.[1])

I have not seen much information about the loss of sodium in the urine following the administration of oral mercurials. These compounds may be well worth their salt, so to speak, but I should like to know whether the sodium is being excreted in the urine, or whether perhaps it is being lost as a result of diarrhea. I have not been impressed by the renal effectiveness of the oral mercurials.

GEORGE C. GRIFFITH (*University of Southern California School of Medicine, Los Angeles, Calif.*): There is urinary sodium excretion from the oral mercurial, and it may be even greater than with the parenteral mercurial. Examples are the cases of 2 of our child patients with rheumatic fever who were in congestive heart failure. They were given parenteral mercurials and then Neohydrin, with no other change in their management. Over a period of 4 weeks, their total urinary sodium output per week was greater during the administration of the oral drug than it had been during intermittent parenteral therapy.

JOHN MOYER: There is little doubt that, when Neohydrin is given in adequate amounts, it produces a definite diuresis, as reflected in the increased excretion of sodium and water. The data presented in FIGURE 1 indicate the response, in terms of sodium excretion, to Neohydrin administered orally. The effect on water excretion is presented in FIGURE 2. Neohydrin, given orally, appears to have very little effect on potassium excretion, as shown in FIGURE 3. Pa-

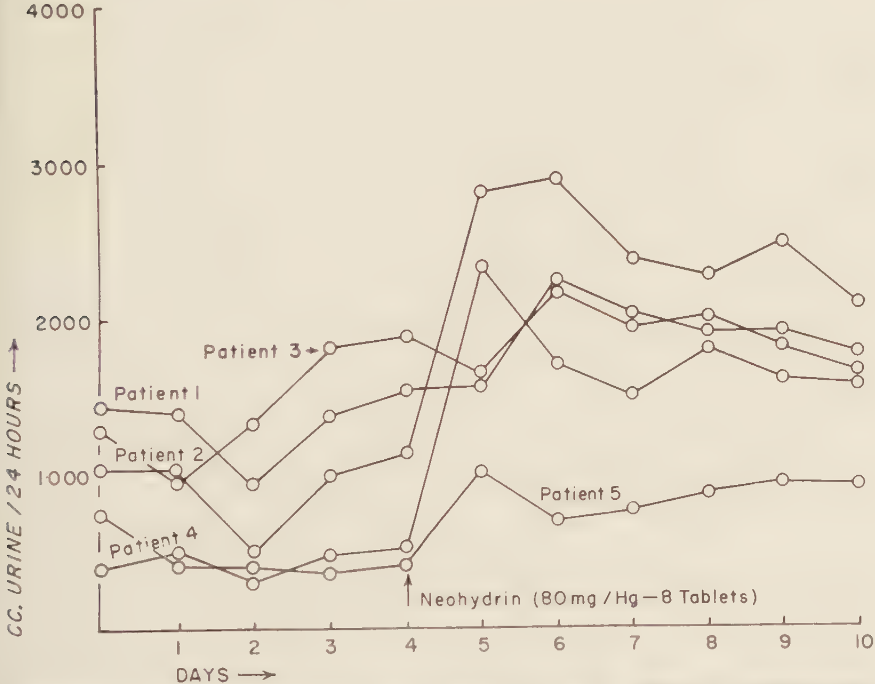


FIGURE 2. The effect of Neohydrin on the excretion of water. After 4 days, Neohydrin was administered, after which there was a sharp increase in the excretion of water. (Reproduced by permission from the *Archives of Internal Medicine.*[1])

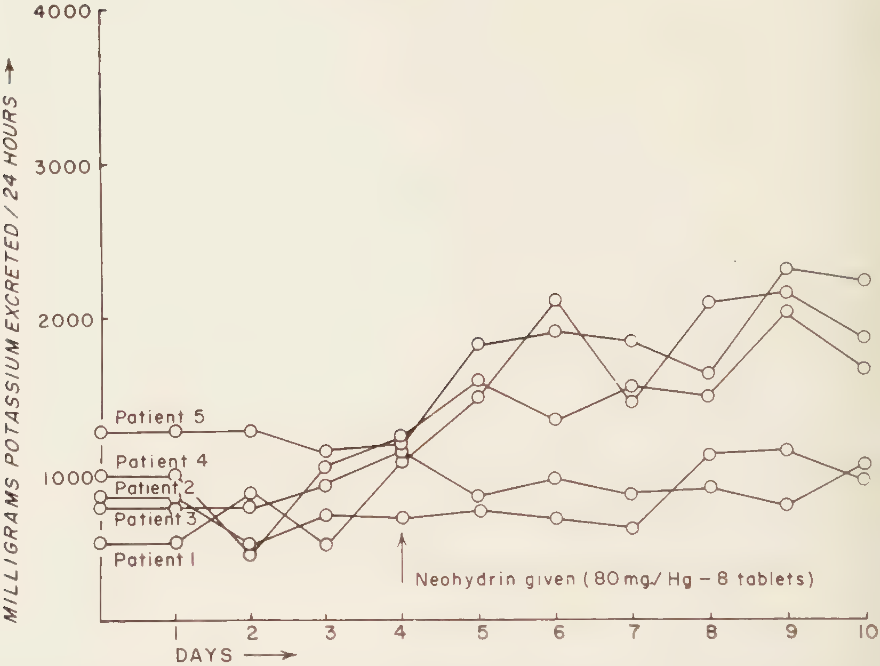


FIGURE 3. The administration of Neohydrin by the oral route. Note the very slight effect on the excretion of potassium. (Reproduced by permission from the *Archives of Internal Medicine*.[1])

tients in heart failure appear to be slightly more responsive than normal subjects.

In our wards we are now completing some controlled metabolic studies that include controlled intake of sodium, water, potassium, and calories. Following suitable control observations, the diuretic is given and its effects on the excretion of sodium, water, chloride, and potassium are measured. We have observed that a dose of Neohydrin of 4 tablets (equivalent to 40 mg. Hg) is a threshold dose and produces an increase in sodium, chloride, and water excretion that is statistically significant.

We have studied the effects of diuretics in patients with heart failure, as well as in those who are apparently normal. We have found that the response of the excretion rate of sodium, chloride, and water and change in weight is distinctly dependent upon dietary sodium. This emphasizes the importance of controlling dietary sodium in patients who serve as subjects of a diuretic bioassay. By an analysis of variance, it has been observed that a noncardiac patient on a high sodium intake, equivalent to 150 mEq., who is not in heart failure will respond in essentially the same manner as a cardiac patient on a low sodium intake insofar as sodium, water, and chloride excretion are concerned. The most consistently significant responses seem to be the increases in sodium and chloride excretion, and the changes in water and body weight are secondary to these changes. The chief difference between the diuretic response of a normal subject on a high-sodium diet and that of a patient in cardiac failure on a low-sodium diet is that diuresis in the cardiac will continue over a prolonged period of time often greater than 18 to 24 hours. On the other hand, the normal subject will usually void a maximum amount during the first 12 hours, following which he will often exhibit some retention of sodium.

Reference

1. Moyer, J. H., C. A. Handley, R. A. Seibert & H. B. Snyder. 1953. Electrolyte, water, and mercury excretion after oral administration of Neohydrin. Arch. Internal Med. **92:** 847–855.

William A. Leff (*Hospital of St. Barnabas and for Women and Children, Newark, N. J.*): Grossman brings up the possibility that once the decompensated patient is brought down from grade III or IV to grade I or II following therapy with parenteral mercurials, the low-salt regimen may be sufficient to maintain him in the improved functional classification without need for continued therapy with oral organomercurials.

This is not the case in our experience, in which we routinely use the low-salt diet. When the severely decompensated patient is recompensated with parenteral mercurials, this has no real effect on the underlying cardiac disease in most cases. Such a patient must be regarded as a potential grade III or IV whose continued maintenance and improved functional capacity is dependent on mercurial diuretics. As Lawrence points out, substitution of a placebo for the diuretic results in renewal of decompensation in these patients.

Robert E. Kaufman (*Lenox Hill Hospital, New York, N. Y.*): I should like to ask how ammonium chloride is used in conjunction with mercurial diuretics. Is it used with all patients receiving mercurials and, after finishing a course of ammonium chloride, how long should one wait before giving the diuretic?

William B. Schwartz (*New England Center Hospital, Boston, Mass.*): If a patient is receiving mercurials at infrequent intervals, for example, once every 2 or 3 weeks, ammonium chloride is not usually a necessary part of the diuretic regimen.

If the mercurial is given more frequently, the tendency for hypochloremia and unresponsiveness to mercurial therapy increases. In this situation, ammonium chloride should probably be used between each injection in order to correct hyperchloremic alkalosis and improve subsequent diuresis. It makes very little difference when the ammonium chloride is given as long as the plasma level is normal or even slightly elevated at the time of mercurial administration. Ammonium chloride may be given for several days after the previous mercurial injection, or for several days preceding the next one.

Maxwell Gelfand (*Post Graduate Medical School, New York University-Bellevue Medical Center, New York, N. Y.*): With respect to additional uses of mercurial diuretics, I have frequently employed these agents for a differential diagnosis between cardiac and bronchial asthma in older patients. There are many cardiac patients who present, clinically, signs of bronchospasm in the lungs, and who also give a history of allergic bronchial asthma. A positive response to the drug in such subjects will clarify the cause of the pulmonary signs. Although this is a simple procedure, it is too often overlooked.

Burgess Gordon (*Woman's Medical College of Pennsylvania, Philadelphia, Pa.*): Several interesting aspects of mercurial therapy have been brought out in this discussion. Those pertaining to disturbances of pulmonary function seem to me to be especially significant.

For example, in compression or relaxation of the lung, as in pneumothorax, there may be interference with pulmonary ventilation due to congestion of the alveolar and bronchiolar structures. Similarly, a disturbance of function may appear in cases with an accumulation of fluid in the air cells and bronchioles, as is sometimes noted in emphysema. These phenomena may occur quite independently of cardiac failure per se. As a matter of fact, the cardiac disturbances could be secondary rather than primary.

In these disturbances it is interesting to note that mercurial diuretics may exert a striking influence in reducing pulmonary congestion, a far more significant action than would be expected from the use of digitalis alone. The value of such diuresis is disclosed in function studies indicating an improvement in pulmonary ventilation, gas exchange and oxygen saturation of the arterial blood.

George C. Griffith: I should like to add to Gordon's remarks an account of a very interesting experience of ours. Patients in chronic congestive failure improved with administration of 100 per cent oxygen, using an intermittent positive-pressure breathing apparatus. Increase in the peripheral arterial oxygen content of the blood promoted diuresis without any change in the established treatment.

Alfred Vogl (*New York University College of Medicine, New York, N. Y.*): It has been most gratifying to me to learn of these important new contributions to a field that I had the good luck to initiate 37 years ago when I noticed the diuretic effect of merbaphen (Novasurol), which had been introduced as an antisyphilitic at that time. I should like to comment on a few of the many fascinating problems presented in these pages.

The emphasis placed in the past on the role of the mercury ion as responsible for the diuretic effect of the organic mercurials has always puzzled me. It was, after all, Novasurol that had shown a potent diuretic action, in striking contrast to the many inorganic mercury compounds then in use as antisyphilitic agents. After our experience with Novasurol we tested these compounds again, found them devoid of diuretic properties, and arrived at the conclusion that the diuretic action was tied to some specific activity of the organic mercurial. This empirical conclusion appears to be corroborated now by the demonstration of the excreted organic mercury complex in the urine, indicating that the molecule traverses the circulation essentially unchanged, acts upon the tubular cell as such, and reaches the urine still basically in its original form.

A very fortunate development is the ever-decreasing toxicity of the newer mercurial compounds. This decrease is obviously not related simply to the amount of mercury which they contain. The original and, apparently, most toxic preparation, Novasurol, contained only 35 per cent mercury, while most of the parenteral compounds introduced since contain 40 per cent. It seems likely that the lessened toxicity is related to the degree of stability of the mercury-carbon linkage. It might, incidentally, be of historic interest to know that a few cases of severe hemorrhagic colitis, 2 of them fatal, occurred at our clinic in Vienna, Austria, immediately after the preliminary report on the astounding diuretic action of Novasurol had appeared. One might well wonder whether we should have dared to continue experimenting with "such a dangerous drug" if those incidents had happened earlier in our series.

The "toxic reactions" that are still encountered from time to time are now recognized to be, in reality, reactions of acquired hypersensitivity to either the mercury as such or, more commonly, to one or more of the specific compounds.

The observations reported here on the long-term, uninterrupted use of oral mercurials challenge some of our traditional concepts of the pharmacology of mercurial diuresis, which appeared to depend on the alternation of brief phases of depression of tubular enzymatic activity and phases of recovery. By this means, the continued effectiveness of the mercurial diuretics, as well as avoidance of permanent renal damage, seemed guaranteed. The studies presented in this monograph clearly indicate, however, that partial inhibition of tubular reabsorptive activity can be maintained over long periods of time without demonstrable anatomical damage to the kidney and without producing renal failure.

In the past 3 decades the treatment of the edematous patient has taken tremendous strides in the direction of lessened risks and improved efficiency. Imaginative research has succeeded in finding better drugs, and critical clinical observation has taught us how to use them most effectively, either alone or in a rational combination with diuretics of different pharmacological mechanism.

It is indeed with a sense of awe that I have been watching, over the years, the continued vigorous growth of the organomercurials from their humble beginnings. I express to the contributors to this monograph my admiration for their carefully planned and painstakingly executed studies on mercurial diuretics.

Printed in the United States of America

MONOGRAPHIC PUBLICATIONS

OF

THE NEW YORK ACADEMY OF SCIENCES

(Lyceum of Natural History, 1817-1876)

(1) The Annals (octavo series), established in 1823, contain the scientific ontributions and reports of researches, together with the records of meetings of the Academy. The articles that comprise each volume are printed sepaately, each in its own cover, and are distributed immediately upon publicaion. The price of the separate articles depends upon their length and the number of illustrations, and may be ascertained upon application to the Executive Director of the Academy.

Current numbers of the Annals are sent free to all Members of the Academy desiring them.

(2) The Special Publications, established in 1939, are issued at irregular ntervals as cloth-bound volumes. The price of each volume will be advertised at time of issue.

(3) The Memoirs (quarto series), established in 1895, are issued at irregular ntervals. It is intended that each volume shall be devoted to monographs relating to some particular department of science. Volume I, Part 1 is devoted to Astronomical Memoirs, Volume II to Zoological Memoirs. No more parts of the Memoirs have been published to date. The price is one dollar per part.

(4) The Scientific Survey of Porto Rico and the Virgin Islands (octavo series), established in 1919, gives the detailed reports of the anthropological, botanical, geological, paleontological, zoological, and meteorological surveys of these islands.

Subscriptions and inquiries concerning current and back numbers of any of the publications of the Academy should be addressed to

EXECUTIVE DIRECTOR
The New York Academy of Sciences
2 East Sixty-third Street
New York 21, N. Y